

SELECT COMMITTEE ON  
SCIENCE AND TECHNOLOGY

**CANNABIS:**  
THE SCIENTIFIC AND MEDICAL EVIDENCE

EVIDENCE

---

*Ordered to be printed 4 November 1998*

---

LONDON: THE STATIONERY OFFICE

£22.60



22501849863



CONTENTS

Page

CALL FOR EVIDENCE

ORAL AND WRITTEN EVIDENCE

Advisory Council on Misuse of Drugs  
Oral Evidence, 7 April 1998

British Medical Association  
BMA—Written Evidence

Professor Ashworth  
Oral Evidence, 27 April 1998

Supplementary Written Evidence—see page 225

Alliance for Criminal Prosecutors, Professor Patrick Wall and Karen Mitchell  
ACT—Written Evidence

Professor Wall—Written Evidence  
Oral Evidence, 28 April 1998

Department of Health  
Written Evidence

Oral Evidence, 2 May 1998

Supplementary Written Evidence—see page 225

Professor John Spring and Mr John Wilson, Rayson Institute  
Oral Evidence, 5 May 1998

Dr David Pearce  
Written Evidence

Oral Evidence, 17 May 1998

Supplementary Written Evidence—see page 225

Multiple Sclerosis Society  
Written Evidence

Oral Evidence, 17 June 1998

Supplementary Written Evidence

Dr William Roberts and Dr David Lambert  
Oral Evidence, 18 June 1998

Dr Lambert and others—Written Evidence

Dr Lambert—Written Evidence

Oral Evidence, 18 June 1998

Supplementary Written Evidence

Mr Neil Montgomery  
Written Evidence

Oral Evidence, 14 July 1998

SELECT COMMITTEE ON  
SCIENCE AND TECHNOLOGY

CANNABIS:

THE SCIENTIFIC AND MEDICAL EVIDENCE

EVIDENCE

|                                    |            |
|------------------------------------|------------|
| WELLCOME TRUST INFORMATION SERVICE |            |
| 08 DEC 1998                        |            |
| ACC. No.                           | 14092      |
| CLASS:                             | Pe A H00/L |

Ordered to be printed 4 November 1998

LONDON : THE STATIONERY OFFICE

£22.60





# CONTENTS

|   | Page |
|---|------|
| CALL FOR EVIDENCE .....   | v    |
| ORAL AND WRITTEN EVIDENCE   |      |
| <i>Advisory Council on Misuse of Drugs</i>  |      |
| Oral Evidence, 7 April 1998 .....   | 1    |
| <i>British Medical Association and Professor Heather Ashton</i>   |      |
| BMA—Written Evidence .....  | 9    |
| Professor Ashton—Written Evidence .....   | 12   |
| Oral Evidence, 21 April 1998 .....  | 18   |
| <i>Supplementary BMA letters—see page 206</i>   |      |
| <i>Alliance for Cannabis Therapeutics, Professor Patrick Wall and Austin Mitchell MP</i>                                  |      |
| ACT—Written Evidence .....  | 27   |
| Professor Wall—Written Evidence .....   | 31   |
| Oral Evidence, 28 April 1998 .....  | 32   |
| <i>Department of Health</i>   |      |
| Written Evidence .....  | 44   |
| Oral Evidence, 5 May 1998 .....   | 49   |
| <i>Supplementary Written Evidence—see page 217</i>  |      |
| <i>Professor John Strang and Mr John Witton, National Addiction Centre</i>  |      |
| Oral Evidence, 5 May 1998 .....   | 59   |
| <i>Dr Roger Pertwee</i>   |      |
| Written Evidence .....  | 64   |
| Oral Evidence, 12 May 1998 .....  | 70   |
| <i>Supplementary Written Evidence—see page 280</i>  |      |
| <i>Multiple Sclerosis Society</i>   |      |
| Written Evidence .....  | 84   |
| Oral Evidence, 9 June 1998 .....  | 90   |
| Supplementary Written Evidence .....  | 100  |
| <i>Dr William Notcutt and Dr David Lambert</i>  |      |
| Dr Notcutt and others—Written Evidence .....  | 101  |
| Dr Lambert—Written Evidence .....   | 109  |
| Oral Evidence, 16 June 1998 .....   | 110  |
| <i>Dr Philip Robson</i>   |      |
| Written Evidence .....  | 117  |
| Oral Evidence, 16 June 1998 .....   | 119  |
| <i>Dr Jan van Amsterdam and Dr Jan Willem van der Laan, Dutch National Institute of Public Health and the Environment</i> |      |
| Oral Evidence, 30 June 1998 .....   | 125  |
| Supplementary Written Evidence .....  | 131  |
| <i>Mr Neil Montgomery</i>   |      |
| Written Evidence .....  | 132  |
| Oral Evidence, 14 July 1998 .....   | 135  |



|  |     |
|--|-----|
| <i>Medical Research Council</i>                      | 143 |
| Written Evidence .....                               | 144 |
| Oral Evidence, 21 July 1998 .....                    |     |
| <i>Home Office</i>                                   | 149 |
| Written Evidence .....                               | 155 |
| Oral Evidence, 21 July 1998 .....                    |     |
| <i>Dr Geoffrey Guy</i>                               | 160 |
| Written Evidence .....                               | 173 |
| Oral Evidence, 28 July 1998 .....                    |     |
| <i>Professor Wayne Hall</i>                          | 183 |
| Oral Evidence, 30 September 1998 .....               |     |
| Written evidence - see page 220                      |     |
| <i>Royal Pharmaceutical Society of Great Britain</i> | 188 |
| Oral Evidence, 30 September 1998 .....               |     |
| Written Evidence - see page 284                      |     |

## WRITTEN EVIDENCE

|   |     |
|---|-----|
| <i>Academy of Medical Sciences—see Royal Society</i>  |     |
| Association of Chief Police Officers .....  | 195 |
| Dr Anthony Blowers, Surrey's Drug Action Team .....   | 197 |
| Mary Brett, Dr Challoner's Grammar School (Boys), Amersham .....  | 201 |
| British Medical Association ( <i>supplementary letters</i> ) .....                                      | 206 |
| Christian Institute .....   | 206 |
| David Copestake .....   | 211 |
| Dr Angela Coutts, University of Aberdeen .....  | 216 |
| Department of Complementary Medicine, University of Exeter .....  | 216 |
| Department of Health ( <i>supplementary evidence</i> ) .....  | 217 |
| Evangelical Coalition on Drugs Executive Committee .....  | 218 |
| Forensic Science Service .....  | 218 |
| Professor Keith Green, Medical College of Georgia, USA .....  | 219 |
| Professor Wayne Hall, Executive Director, National Drug and Alcohol<br>Research Centre, Australia ..... | 220 |
| Professor John Henry, Imperial College School of Medicine / Royal College<br>of Pathologists .....      | 223 |
| Dr Anita Holdcroft, Imperial College School of Medicine .....   | 224 |
| Independent Drug Monitoring Unit .....  | 225 |
| Institute for the Study of Drug Dependence .....  | 262 |
| International Drug Strategy Institute .....   | 264 |
| Edward H Jurith .....   | 265 |
| Dr David Kendall, University of Nottingham Medical School .....   | 265 |
| London Medical Marijuana Support Group .....  | 269 |
| Medicines Control Agency .....  | 272 |
| Dr Tod H Mikuriya .....   | 273 |
| National Drug Prevention Alliance .....   | 274 |
| NHS National Teratology Information Service .....   | 279 |
| Professor David Nutt, University of Bristol .....   | 280 |
| Dr Roger Pertwee ( <i>supplementary evidence</i> ) .....  | 280 |
| Royal College of General Practitioners .....  | 280 |
| <i>Royal College of Pathologists—see Professor John Henry</i>   |     |
| Royal College of Psychiatrists .....  | 281 |
| Royal Pharmaceutical Society of Great Britain .....   | 284 |
| Royal Society / Academy of Medical Sciences .....   | 293 |
| Dr Fred Schon, Mayday Hospital Croydon and St George's Hospital .....                                   | 303 |
| Dr Colin Stewart, Dundee Limb Fitting Centre .....  | 304 |
| Young Christian Democrats .....   | 305 |

Extensive lists of references are not reproduced; to trace references, please contact the Committee Office (0171-219 6075).



Written evidence from the following is not printed, but is available for inspection at the House of Lords Record Office (0171-219 5316):

Anonymous  
J Brown  
S Cooke  
R Creasey and J Sayers  
P Davidson  
M Davies  
S Day  
C Fell  
L Gibson  
M Humphreys  
D Lewis  
A Phillipson  
P Rigby  
E Rorison  
Dr P Shaw  
Councillor C Simpson, Aberystwyth  
L Standen  
G Vincent

## CALL FOR EVIDENCE

*Issued April 1998*

Sub-Committee I has begun an enquiry into the science behind the arguments over the use of cannabis and its derivatives for medical and recreational purposes. The Committee will receive evidence in writing and in person, with a view to making a report to the House of Lords by November 1998. You are invited to submit written evidence on any or all of the following questions:

- What are the physiological effects (immediate, long-term and cumulative) of taking cannabis, in its various forms?
- What are the psychological effects?
- How do these effects vary with particular methods of preparation and administration?
- To what extent is cannabis addictive?
- To what extent do users develop tolerance to cannabis?
- What is the evidence that cannabis in its various forms has valuable medicinal actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?
- On the basis of the answers to these questions,
  - How strong is the scientific evidence in favour of permitting medical use?
  - How strong is the scientific evidence in favour of maintaining prohibition of recreational use?

The Committee will **not** consider the following: prevalence of cannabis use; behavioural and social aspects of drug-taking; law, law enforcement, and the relationship between drugs and crime; public education; testing for cannabis use at the roadside or in the workplace; and the extent to which cannabis constitutes a gateway to a “drugs culture”.<sup>1</sup>

<sup>1</sup> Some of these matters are under consideration by the Independent Inquiry into the Misuse of Drugs Act 1971 established by the Police Foundation: details from W Saulsbury, Police Foundation, 1 Glyn Street, London, SE11 5RA.





# MINUTES OF EVIDENCE

TAKEN BEFORE THE SCIENCE AND TECHNOLOGY COMMITTEE (SUB-COMMITTEE I)

TUESDAY 7 APRIL 1998

---

Present:

Kirkwood, L.  
Nathan, L.  
Perry of Walton, L.  
(Chairman)

Porter of Luddenham, L.  
Soulsby of Swaffham Prior, L.  
Walton of Detchant, L.

---

## Examination of Witnesses

PROFESSOR DAVID GRAHAME-SMITH, Chairman, Advisory Council on Misuse of Drugs, PROFESSOR MALCOLM LADER, Institute of Psychiatry, Chairman, Technical Sub-Committee, Advisory Committee on Misuse of Drugs, PROFESSOR GRIFFITH EDWARDS, National Addiction Centre, and DR MORFYDD KEEN, Consultant Psychiatrist, were called in and examined.

### *Chairman*

1. Perhaps, Professor Grahame-Smith, would you introduce your colleagues to us and tell us what they are particularly interested in.

(*Professor Grahame-Smith*) First of all, Dr Morfydd Keen, who is a consultant psychiatrist and runs a drug addiction clinic in Cardiff. Professor Griffith Edwards, well known in the drug misuse field, is at the National Addiction Centre and was director of that. Then Professor Malcolm Lader, who is in the Institute of Psychiatry and is Professor of Clinical Pharmacology at the Institute of Psychiatry and Chairman of our Technical Sub-Committee of the Advisory Council.

2. Would there be anything you would like to say before we start asking questions?

(*Professor Grahame-Smith*) I think one of the things that might be helpful is perhaps for me to say a few words about the Advisory Council.

3. Yes?

(*Professor Grahame-Smith*) It is a statutory committee which in essence was set up by the Misuse of Drugs Act 1971 to advise ministers on all aspects of drug misuse. I will not go into the detail, there is a lot of detail, but it involves all aspects of drug misuse. Cannabis is a Class B drug and, as such, comes under the Council's responsibility. From time to time, that is at least every year or every six months, as with all other drugs, the Council considers the statistics available on the misuse of cannabis and it has to consider largely anecdotal data on the psychological, physical and social harmful effects of the drug and changes in the pattern of its use and changes in the international scene as regards the misuse of the drug which have an impact on the United Kingdom and the misuse of drugs in the United Kingdom. There have been two reports from the Council on cannabis in the past and in the recent past we reviewed skunk weed which is a particularly potent form of cannabis made by a hydroponic method. We were concerned—this was fairly recently—about the potential of this form of cannabis for producing psychoses. This was in Professor Lader's Technical Sub-Committee. We decided then to have a re-look at the harmful effects of cannabis. The Department of Health took it upon itself to commission a number

of reports on various aspects of the harmful effects of cannabis. They are being written, and I think I wrote to you about that.

4. Yes.

(*Professor Grahame-Smith*) They are being written and no doubt you will be able to see them or the people who are writing the reports. I think they are nearly ready but we have not seen those yet so I cannot refer to them. We have considered within our reports on the criminal justice system, and on drug education in schools generically the matter of cannabis, though at no time in those reports have we stated specifically matters in relation to cannabis. We have been concerned with cannabis as part of the multi-drug misuse scene as well. That is what the Council is about.

5. [Unallocated]

6. [Unallocated]

7. Would you comment on the various medical applications that have been proposed for cannabis, especially how far you feel any of them warrant further study?

(*Professor Grahame-Smith*) I speak as one who was on the Committee on Safety of Medicines for 12 years and who has seen the problems and details of actual drug development in relationship to the use of medicines. There are many questions which have to be answered really before one moves into the use of cannabis, I believe, for the treatment of any medical condition. What is the formulation that is to be advised if the drug is going to be prescribed, how are you going to predict its potency for any particular use, what is the mode of delivery going to be for the patient, how are they going to know that they are getting the best mode of treatment, what is the predictability of blood levels and how is the purity of the drug substance going to be ensured? These are all rather boring details, but nevertheless absolutely essential to the proper use of the medicine. For the moment, before going into the particular conditions, those problems have to be met head on. I do not want to go into those any more as I am sure you are fully aware of them. I did want to say that it is not quite as straightforward as one might think. Perhaps Professor Lader would like to tell us a little more about the specific conditions.



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Chairman Cont]

(*Professor Lader*) There have been several conditions in which therapeutic effects have been claimed. I think the most important one is in the treatment of nausea and vomiting following cancer chemotherapy or radiotherapy. Many of those claims were made some years ago before we had available some of the more modern treatments. I refer specifically to the so-called 5HT 3 blocking agents which are very powerfully anti-emetic. I think therefore that what one would be dealing with in that indication would be a small sub-group of patients who either could not tolerate or at least do not respond well to the 5HT 3 inhibitors and there would be other medication they might try. I would also like to point out to your Lordships that there is a drug available called nabilone which is a synthetic cannabinoid. From my knowledge of it, it seems to have the therapeutic profile of cannabis and it is licensed and available, but, to the best of my knowledge, and I am not an oncologist, it is not widely used. It is used only occasionally in patients who really fail to respond to anything else. So I think we already have a compound available. There may be claims that take account of this in another way, like smoking cannabis has therapeutic benefits not possessed by a regular synthesised oral medication. I think those claims would have to be directly addressed and that raises problems of control, because it would be rather difficult to not so much control the smoking, because you could get a preparation which did not release the cannabis, but control the other effects of which sedation and euphoria would be the most prominent. I think there is a way in which one could look into these claims, but I feel it is going to be very much a minority usage and there would be practical problems about who would take up the development of cannabis in this form. Of the other indications which have been suggested, one is in the treatment of glaucoma, lowering abnormal high pressure in the eye, but I do not think there is a great deal of evidence suggesting much efficacy there. There is also the possible use to combat motor spasticity in patients with multiple sclerosis. I think this claim again could be looked at because the treatments which are available like baclofen and benzodiazepines are of limited effectiveness. The fourth indication to which attention has been drawn is an increase in appetite in patients with AIDS. The problem as I see it there is that cannabis is known to affect the immune system. There are receptors in the immune system which cannabis substances bind to and this would be an unknown factor because you might give the patients short-term benefit but long-term damage, because you would suppress the immune system even further. As far as the technical development is concerned, this is feasible. The problem is of course quality control. Cannabis has in fact over the last 20 years probably increased in potency at least ten times. Some of these new preparations are very highly saturated with cannabis; 20 per cent is the sort of figure one sees. The problems of making sure the preparations are the same from batch to batch would need addressing, particularly as we are dealing with a mixture in the natural substance. There are 60 cannabinoids of varying potency in cannabis smoke so that the technical problems are fairly daunting.

8. Would you like to comment further on the special difficulties involved in conducting clinical trials with cannabis?

(*Professor Grahame-Smith*) The problems actually hark back to what I said previously, that to test something you have to test the formulation, so we start there with that problem again, that you have to know what they are testing. That, to my mind, has not been solved yet. Professor Lader disagrees with me a little bit on this, I think, but to my mind carrying out a double blind randomised placebo-controlled clinical trial on cannabis is not easy because of the psychological effects that the drugs would have and the unblinding which immediately occurs when you give the drug. Although that is the gold standard, it is not always necessary to do that and you can do more open studies and make observations but you have to do them on a large number of people, I believe. Personally, I do not see any fundamental problem in doing clinical trials on some sort of cannabinoid preparation. It would be quite possible to do that and it was done for nabilone and its effectiveness in cytotoxic drug therapy induced emesis was established and it has a licence for that. It is possible, but it is quite difficult. Of course somebody has to pay for those studies. The question is whether you get anybody to take it on. There are quite a number of detailed questions around the problem of actually doing clinical studies on cannabis. Professor Lader would like to remark; he has some ideas how to keep them double blind actually.

(*Professor Lader*) The work that needs to be explored would be not to control the use of the cannabis against an inert dummy but to try and control it against an active placebo, give something which would have some of the properties of cannabis in order to blind this, at least to some extent. This is a problem which comes up with drug use in psychiatry quite often because the drugs have more than one action and you have to try and mask or at least control the secondary action.

*Lord Porter of Luddenham*

9. We are talking about cannabis and of course that is one of the difficulties, is it not, because what is cannabis? If one is going to do a proper control test, does one not have to do it on a pure substance like THC? Is that possible? You cannot smoke THC, can you, because you would be decomposing it, you would have secondary action?

(*Professor Grahame-Smith*) I believe you could actually and then that would mean putting the THC on tobacco and smoking. It is possible to do. I could put heroin into tobacco, you could smoke it.

10. You are back in a mess, are you not?

(*Professor Grahame-Smith*) Yes.

11. What about eating or drinking?

(*Professor Grahame-Smith*) You can eat THC. I suppose the closest to smoking would be some form of nebulised THC. To get to that point, to formulate it, to be nebulised, to get in, is a major scientific pharmacological task. I am not saying it should not be done but it is not quite straightforward.

12. And expensive.



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Lord Porter of Luddenham Cont]

(Professor Grahame-Smith) Yes, expensive, yes.

(Professor Lader) THC is available in the United States. It is licensed over there as a pure substance.

13. Then how do you test it?

(Professor Grahame-Smith) It is taken by mouth.

14. That is presumably a well-controlled experiment and you know the number of milligrams.

(Professor Lader) Yes, it is a pure substance.

15. Yes.

(Professor Grahame-Smith) Could I say that I do not know what part the pharmacokinetic profile, that is the rise and fall of plasma levels, of cannabis plays in its pharmacological effect. Now, when smoking a joint, the plasma level, brain level of the drug, goes up really quite quickly and decays quite quickly. The profile of eating cannabis is quite different because it takes longer to get in, it has to go through the liver, with some metabolism of the drug and so on. The profile you get in the brain and in the blood will be quite different. I presume the pharmacological effect in the person taking it will therefore be different. Even at that simple level there is quite a number of unknowns in terms of treatment of a disease.

Lord Kirkwood

16. Given that there are great difficulties in conducting good and acceptable experiments on cannabis and its derivatives, that is not a good reason for not doing the work. The evidence is there is very little research work being done in this field. The question is why is that? Is the funding just not available or is the interest not there?

(Professor Lader) It would come into the category of what are called orphan drugs, and there is no great commercial advantage in developing them. We have heard about the problems of standardisation and drugs are licensed on efficacy but also quality. If you have something which is difficult to standardise then you could expend a great deal of money trying to standardise the preparations to satisfy the medicines legislation on this. There is a feeling that this is a relatively small proportion of patients and that once they have been treated by experts in the control of nausea, vomiting or spasticity and so on, you are left with a rather small residue which is not commercially viable for any drug company. The funding would have to be in an unusual way, maybe special funds in some way, but certainly the pharmaceutical industry would not be very interested.

17. It would have to be government funding, MRC?

(Professor Lader) Whatever.

Lord Walton of Detchant

18. We were told that nabilone was introduced or developed by a drug company in the 1970s and that they have not pursued it because of its comparative lack of advantage in comparison with other drugs but also because its absorption is so uneven when taken by mouth and so unpredictable. Would it not be possible to design cross-over trials in which, for example, in studying the anti-emetic effect, you

compare it against serotonin antagonists on a cross-over basis and the same in multiple sclerosis for spasticity? Incidentally, you stressed the point, there is nothing in the published works to suggest that any of the cannabinoids have any beneficial effect upon multiple sclerosis in relation to the progression of the disease and it is purely a treatment which has been suggested for symptomatic relief of spasticity. The question I would like to ask you is whether you feel that the euphoric effect might also in advanced cases of multiple sclerosis have a beneficial effect upon depression, which so often occurs in late MS, and is that possibly one of the reasons why patients with MS have suggested that they would wish to use this particular remedy?

(Professor Grahame-Smith) That they feel better?

19. Yes.

(Professor Grahame-Smith) Euphoric. I think Professor Edwards may have a view on that.

(Professor Edwards) As a footnote, this is an area where my colleagues have far greater expertise than I do, but I would ask what is the first level reason for contemplating clinical investigation? Is there a strong *prime facie* case for diverting MRC money in this direction? The evidence we have is anecdotal from people who are themselves sufferers from, say, MS. I do not for a moment dismiss anecdotal evidence, and to say merely anecdotal seems to me ungenerous. There is a number of repeated anecdotal reports. I believe in the face of such evidence it would be reasonable to investigate the matter, but I do not believe it would be reasonable to go through a controlled trial. A controlled trial is an expensive paraphernalia and it means giving, with informed consent, a drug to patients on a blind basis. I think ethical questions, for instance, whether one has any right to introduce patients in that way on a significant scale to cannabis or a cannabis preparation, are still very open, whether it is ethically acceptable. We do not really know much about the toxicology of cannabis. We do not know if we are introducing things which are potentially dependence-producing drugs and in three months' time we are going to be in medical and legal difficulties if they claim they have been introduced to a drug which is now very difficult for them to stop taking. I think that long before going to a controlled trial, one should be doing a small series of open clinical investigations with repeat and careful observations on the individual patient. That seems to me to be possible and I understand from the Home Office that there is no legal bar on such medical investigation. I think a controlled trial is somewhat down the line.

20. If I could come back on that point, it would not be difficult in patients with MS who had severe spasticity to do a cross-over trial in which you gave the nabilone for a period and then a wash-out period and then you could have the effect of baclofen or benzodiazepines?

(Professor Edwards) That is absolutely possible. I would also caution slightly about the rules for introduction of a new drug, well known to my colleagues who work with CSM and so on. I think from my point of view I would caution also about introducing a new drug which may not be more effective than an old drug but which may have greater



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Lord Walton of Detchant Cont]

potential for diversion to misuse. Without pressing the panic button, one must be aware that if cannabis or cannabis preparation became widely available on prescription, you are inevitably opening up the possibilities of misuse. When I was around in the 1960s, I was asked by the Medical Defence Union to give advice on a doctor who had been inviting patients to test cannabis which was then available, pour it on tobacco, roll up and light a match. There are real possibilities of diversion to misuse for the drug.

21. How safe is cannabis by comparison with other medicinal products? Do you believe that it may produce a reversible psychosis which ceases when the cannabis is withdrawn or do you take the view that some others appear to take that it may precipitate the development of schizophrenia in susceptible individuals? Secondly, are you convinced that heavy use over a long period does produce significant cognitive decline or so-called amotivational syndrome?

(Dr Keen) As far as a short-lived cannabis psychosis is concerned, I have seen cases which have cleared up completely and have reappeared when the person starts smoking cannabis again. As far as whether it triggers off schizophrenia in people who are vulnerable, what certainly is true is that it makes the illness of schizophrenia worse in the people who smoke it. This is of great and increasing concern amongst my general colleagues in the hospital. I am sure you are aware the question of dual diagnosis of substance abuse and psychiatric illness is a very vexing one. As far as long term cognitive effects are concerned, we have a copy of a paper as yet unpublished by Nadia Solowij which does show some subtle long-term cognitive deficits in people who have been smoking cannabis for some time. As Professor Grahame-Smith has said, a lot of this evidence is anecdotal and comes from observation of patients over a number of years. I do feel that the frequency of the taking of the drug, the way in which it is taken, the type of cannabis preparation that is taken, is important; it does appear to have a dose-related effect. People who smoke very heavily are more likely to get into difficulties than people who smoke more occasionally.

(Professor Edwards) When one is dealing with psychotic disturbance—that seems to me such an awkward word—what I mean by this is losing touch with reality, the trees moving as you walk by them rather than you moving, your arm floating, funny things like that happening, one is dealing with a spectrum of disorders. If you look at surveys of social users of cannabis, up to 20 per cent of them will give a report of minor experiences, including mood disturbance, which they describe as paranoid disturbance and anxiety disturbance. One has a firm base of the bottom of an iceberg, as it were. One can certainly show, not uncommon, some form of minor spectrum disorder. You have to use different research techniques which have included surveying people on acute admission to a psychiatric emergency centre. There was one notable paper from South Africa a few years ago. You can identify clinically features of acute cannabis psychosis which are identified by positive urine tests for cannabis, that does not prove

it, but by the rapidity of appearance, if somebody appears to be very ill and you wonder whether it is acute schizophrenia and acute mania, and 36 hours later they are better, that builds on the spectrum. It is not dangerous, but it is incommensurate and it absorbs a bit of resources. If you have those two layers, it is a question of what happens further with longer use or heavier use with a drug which is cumulative. I have to say I do not know. My friends in India say with heavy cumulative use they may see someone going into a state and staying that way for days. As regards brain damage, the lesson I draw here particularly is the need for caution and the fact that we are very much at the growing edge of knowledge. So many things, if you had asked us last year we might have said something more bland on cannabis than we would this year. Some of the evidence which comes in month by month makes me more worried, not less worried. Thus Nadia Solowij's brilliant monograph using very advanced techniques suggests that impairment in so-called executive brain function—which will not be picked up by an ordinary paper and pencil test—after three or four years of use with normal so-called social abuse—what goes as social use in Australia—does not clear when the person is off the cannabis. I think there are reasons in what we know of possible neuropathology of the drug to make that not improbable. I think today—I would not have said so a year ago—there is evidence that you can get subtle impairment of the brain function which may be important in some jobs which will be important if you have large-scale use but that is what we know today; what we will know tomorrow may be different.

22. If there is acute psychosis which may result from cannabis, maybe that includes delusions and hallucinations, may it lead to a mistaken diagnosis of schizophrenia if the doctor is not aware that the patient has been using cannabis?

(Professor Edwards) That most certainly does happen. It is very important in training psychiatrists that they know more of this complaint.

Lord Nathan

23. Dr Keen referred to heavy use of cannabis and really in the context of frequent prolonged, use so many times a day for so many months. Is there a situation with cannabis that it can be actually stronger or weaker?

(Dr Keen) Certainly that is true as well. You have heard mention earlier of skunk weed cannabis which has a very much higher concentration of THC. I am quite convinced that this is likely to induce psychotic reactions. In fact, patients describing it say, "You do not want to take that strong stuff because it really does make you psychotic". They recognise that themselves.

Lord Porter of Luddenham

24. Can you say that there is no difference between taking a small dose of a strong proportion of THC compared with a large dose of a weak concentration of THC?



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Lord Porter of Luddenham Cont]

(Dr Keen) You would need to add it up over the day. I suppose there is a case for saying if you smoke ten cigarettes with two per cent and one with 20 per cent then you have the same cumulative effect. I would think that the immediate effect of the larger dose on performance is likely to be greater.

25. But worse in the long run or not? More harmful?

(Dr Keen) I am afraid I cannot answer that.

(Professor Lader) The first point I would like to make is that I do not think cannabis is in a category of its own as far as this relationship to psychiatric disturbance is concerned. We have amphetamines, for example, which are very similar in this respect, but they have a different pharmacology but have very acute toxic effects which are probably related to peak concentration. So if you take a deep breath of a very high concentration you are more likely to precipitate toxicity than precipitate a psychosis. In the longer term it is probably the cumulative dose that counts. There is evidence that the tendency to take cannabis in a higher dose is also related to the tendency to develop a psychotic illness, psychotic predisposition. Therefore, there may be a relationship between the two which is actually a fortuitous one, not a direct relationship. There is other evidence, certainly in the patients that I see—and I practise in a part of London where cannabis is part of the culture—the patients take the cannabis as a self-medication to try and dull their terrible symptoms which are going on in the brain in patients with a natural psychotic illness. There is a very complicated issue here. We have got both the peak concentration and the cumulative use and both are important in different respects.

Lord Soulsby of Swaffham Prior

26. How important is the cultural context of cannabis use in determining its effects?

(Professor Edwards) I would start by saying that culture begins at home, not just exotic places. I sometimes get a little bit tired of debates at Oxford and Cambridge Union where it is assumed that the only cannabis users are members of elderly universities and they use it in a gentlemanly fashion. Down in Camberwell the average denizen is not a member of an older university and they use their cannabis differently. In recent survey work unpublished, which I have seen, it is possible to pick up people round my patch of London who use 20 reefers a day. That is unthinkable in some university setting in the polite middle-class smoking-jacket world. It is unthought of and seen as probably inconceivable. The culture where people are otherwise using drugs for drug effects, very heavy use, is culturally determined and culturally proposed, including the use of bongs. You get very heavy and very sustained use of cannabis going on. If you try to learn a lesson, which I think you should do with extreme caution, by looking at another aspect of the culture which is history, of course cannabis was widely used medicinally in this country in the last century. I picked up a report from the 1880s of a GP writing to *The Lancet* who developed acute psychotic illness when treating himself for his sciatica with cannabis. People were well aware at that stage that it

was an unpredictable drug. Then better drugs came along, aspirin, much better pain killers, better ways, it was used for withdrawal from dipsomania, it was the treatment used for treating mania unbelievably. Better drugs came along and it naturally wasted away. I think I would have learnt something from history but one does forget the history of drug use. In relation to culture what fascinates me is that, say, in Egypt the assumption is that nice people do not smoke cannabis, well some do, but it is seen as a slum drug and it is seen as a slum tranquilliser. In modern Africa, the well-known phrase is the “kiff-happy beggar”. What we expect to get out of our drugs partly we will succeed in getting out of our drugs, but I think we forget at our peril the picture of the drugs as they exist in countries where there has been very high level use. Evidence from the old WHO report is that you can easily get up to ten times the expected European use in countries like India and Egypt. In those countries the drug tends to have a bad reputation. It is assumed by psychiatrists on very dubious evidence, I must say, friends in Jamaica assume that a certain proportion of the work of Bellevue Hospital there is related to the treatment of cannabis psychosis which goes on. I think simply to sensitise one’s mind to produce, or modestly to persuade us that in this cultural country we have not seen it all, there is quite something to be said for a world tour, an historical tour.

Lord Kirkwood

27. Is cannabis an addictive drug? If it is an addictive drug, where do you place it in relation to other drugs of addiction? How do you measure this? What scientific measurements are there available to measure such effects to rank drugs?

(Professor Grahame-Smith) Could I just kick off on that because that is obviously a very, very important question about the drug. The Department of Health produces this Bulletin of Drug Misuse Statistics every six months. This is the latest one up to September 1996. I only got it the other day. It is often said, of course, that we do not really know how many people are misusing cannabis because they do not come to drug treatment services or agencies and so on. Flipping through this it turns out, and I was very surprised, that in 6 per cent of contacts with agencies reported to the regional drug misuse databases, the main drug of misuse is cannabis. That seems to me to be a very high percentage for a drug that is generally assumed not to cause great problems. I know Dr Keen has a word to say about the addictive side of cannabis. I was frankly surprised by that high percentage.

(Dr Keen) Yes, my Lord Chairman. We certainly are referred a number of people, both by self-referral and by general practitioners, who are concerned by their use of cannabis and cannot stop. They describe irritability, insomnia, bad dreams and anxiety when they are deprived of the drug if they have smoked it long enough. Like everything else, a very important fact is that it is variable from one person to another. My feeling is that people who say it is not addictive, would be like the lady who drinks a glass of sherry once a month and would not be able to believe that



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Lord Kirkwood Cont]

alcohol was addictive. Again, I think it is related to the frequency of use. If they use it often enough then they are going to get to a stage where they are psychologically dependent and in some cases will experience emotional and physical distress when they try to stop. That, by definition, is dependency.

(Professor Edwards) I agree with all of that. Again I want to emphasise the sense of being at a growing edge of knowledge. Some years back, it was the perceived wisdom that cannabis was not dependence-inducing and I certainly am on record for taking that view. I would today have to change my mind. We are in a rapidly changing field of knowledge. The mistake is to concentrate only on physical symptoms. Dependence is a complicated psychobiological syndrome. It is really a strong habit. If you look at the surveys which are coming in from high dosage areas like the Queensland coastline, you find that 10 per cent of long-term users regard themselves as being dependent on strict objective criteria, DSM4 criteria. It is not a rarity. That appears with probably 5 per cent of people in western countries who use alcohol, 5 per cent of males, a smaller percentage of females, who would consider themselves dependent or long-term users. In the United States the National Institute of Drug Abuse has recently set up the first controlled trials on treatment for cannabis dependence. Cannabis dependence is becoming a real clinical issue. It matters socially because one's choice as to whether one quits or continues is impaired, as it is with cigarettes, once you are a dependant.

Chairman

28. How does it compare with dependence on tobacco?

(Professor Edwards) I think nicotine is a far more dependence-inducing drug. Nicotine is one of the most dependence-inducing drugs. Anyone who uses nicotine for more than a few packs is really risking dependence. Clearly that is not so with alcohol and it is not so with cannabis. Thus, it is so easy, as the Chairman was saying, to dismiss the danger and go on the one sherry analogy. I would say that the scientific evidence, the experimental evidence, epidemiological and clinical evidence, all have the confidence to show cannabis is a drug of dependence.

29. They changed the definition of addiction, did they not, from the previous definition which involved physical withdrawal symptoms—

(Professor Edwards) That is right.

30.—to not requiring that to define addiction.

(Professor Edwards) I think we do know rather better what we are talking about.

Lord Kirkwood

31. Your statement earlier, was that on the basis of the patient him or herself saying they are addicted? I do not see how that can be used as a measurement; it is just the belief of the individual involved. Is there any other more objective way?

(Professor Edwards) It is not just saying "you feel you are dependent". The whole of scientific

epidemiological research has developed beyond belief over the last 20 years. In the old days how did you diagnose schizophrenia? You can still only diagnose by listening to what the person says, but in terms of a very carefully structured interview with scoring systems. The person as the witness is still the only clinical material you have got. It is not feeling their pulse or taking their blood pressure. There are now very exact measures for defining a case and making a diagnosis. The so-called DSM4, which is an American system, is widely used and these criteria have been applied countless times.

32. There is a generally accepted definition, that is what you are saying?

(Professor Edwards) Yes, an internationally accepted operational definition.

Lord Porter of Luddenham

33. Would you say a word to us about any special problems or dangers which may be associated with the newly developed and more potent forms of cannabis, either synthetic or, as Professor Grahame-Smith mentioned, skunk weed?

(Professor Grahame-Smith) Professor Lader, as I say, chairs the Technical Committee which dealt with skunk weed, so I might refer that to him because he spent some time considering that particularly potent form.

(Professor Lader) Again we are talking here about vastly increased dosages which people are getting from smoking cannabis which is available now and it is done by hydroponics, strains of cannabis which were unheard of 20 years ago.

34. This is higher doses of THC essentially?

(Professor Lader) Yes, it is the whole panoply of cannabinoids. It is the same sort of profile, but there are much higher concentrations so that the flowering tops, which have the highest concentrations, can have 10 to 20 per cent of cannabinoid substances. One of the questions which came up was why does the plant produce all these and the best answer is that if animals or insects chew on these plants, they do not chew very far before they get intoxicated and there must be some biological advantage, at least in the older forms. There is very little doubt that dependence is much more of a risk for the high-dose usage and the sort of figures which are now coming through are again something like 5 to 10 per cent of heavy users, daily users, will show withdrawal symptoms, and that is one indicator of dependence, as well as drug-seeking behaviour. There is evidence that the cardiovascular effects are much more marked, for example, a tremendous increase in heart rate. Elderly people, for example, where it has been used in a sort of quasi-therapeutic context, can actually develop cardiac side effects, such as angina, so there is a danger with that. The bronchitis which you get from smoking cannabis is probably not increased and that is probably just the residues in the leaves, but certainly the whole scale of both possible therapeutic effects, but certainly of side effects, that is all calibrated much higher with these newer preparations.



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
 PROFESSOR MALCOLM LADER,  
 PROFESSOR GRIFFITH EDWARDS AND  
 DR MORFYDD KEEN

[Continued]

[Lord Porter of Luddenham Cont]

35. So any special problems are really to do with the amount in the new materials, not new substances particularly, but more of them?

(Professor Lader) Well, to the best of our knowledge, but again, as I mentioned, with so many substances, it is not impossible that some new substances have been synthesized by the plant which have different properties, including toxic properties.

Chairman

36. I am right, am I not, in thinking that in the whole range of cannabinoids, there is nothing that has anything like the potency of THC?

(Professor Lader) Well, the metabolite of THC is even more potent.

37. Yes, I understand that, but not in the plant?

(Professor Lader) Well, again I am not sure that there is enough systematic data looking at each of those constituents. It would be difficult to do and you would have to decide which preparation you were using, whether you were going to be using mice aggregation or whether you were going to be using subjective effects in humans, and you would have a tremendous problem of relative assays of all these different constituents, but, to the best of my knowledge, the Delta 9 THC does have the greatest effect in human use, yes, my Lord.

Lord Porter of Luddenham

38. It has the greatest effect because it is there in the highest concentration?

(Professor Lader) No, it is just that its intrinsic effectiveness is high in the way that, say, morphine is a better analgesic than aspirin.

39. Are there cannabinoids which are there in stronger concentrations than THC?

(Professor Lader) No. There were four main ones, but the Delta 9 THC is usually the most concentrated.

Lord Walton of Detchant

40. Many years ago, as a medical student, I was taught that there was a difference between a drug of *dependence* upon which you became dependent and which produced withdrawal effects when you stopped it, and a drug of *addiction* upon which you were also dependent, but which required increasing doses to produce the same clinical effect. Is that a valid distinction or is it one which is no longer held?

(Professor Grahame-Smith) I think Professor Edwards is an expert on the semantics of drug addiction and drug dependency.

(Professor Edwards) My Lord Chairman, I would spare you the semantics. I think it is more than semantics and again knowledge has grown since our medical school days. Dependence means a strong habit, a strong drug-seeking habit, and some of the drugs will some of the time be associated with escalation in use, thus with benzodiazepine, on which Professor Malcolm Lader is a leading expert in this country, you can become dependent with no escalation, but, on the other hand, young people may

inject temazepam and use it as a street drug, so there is a great mix of habits, but the core thing is strong habit.

41. And the other point arising out of this is that, from what you have already told us, it would appear that if you look at the effects of a single cannabis preparation of whatever nature, there is a close correlation between the actual frequency and amount of use, on the one hand, and the likelihood of dependence and of possible adverse consequences, on the other. Is that a linear relationship or is it to any extent related to the individual's personality profile?

(Professor Lader) I think, my Lord, that certainly there has been a great controversy certainly in the benzodiazepine field which I know best as to whether people become dependent because they are predisposed to become dependent or whether they become dependent because of the particular usage of the medication that they are taking. Now, I think the answer is a bit of both. There are people who are more predisposed for impulsiveness or gratification and so on and they are at greater risk of becoming drug-dependent. Implicit in the question is also whether there is a threshold, in other words, is there a safe usage of a drug beyond which you then are at risk? My view is that it is probably a linear relationship in the absence of better evidence and that there are people who are at risk even at low usage and as you increase the dose, then a higher proportion of people are likely to become dependent.

Lord Nathan

42. Is there a question as to the part that cannabis plays in the overall pattern of multi-drug abuse and that, I suppose, includes the question about combinations of drugs, perhaps combinations also with alcohol?

(Professor Grahame-Smith) I think it might be interesting, my Lord Chairman, if Dr Keen perhaps just told us about her experience at the coalface of multi-drug misuse in which cannabis is actually involved in a drug addiction clinic.

(Dr Keen) I would say that it is the exception for someone who presents to the clinic with an amphetamine problem, an opiate problem or whatever not to smoke cannabis as well, and also for some people who drink alcohol also to smoke cannabis. There is evidence of the potentiating effect of alcohol if you smoke cannabis with it and certainly evidence from the States of driving, for example, being made worse if you smoke cannabis as well as drink alcohol. I have been doing a straw poll in recent weeks of a number of patients who used to smoke cannabis, but have stopped and asking them why they no longer smoke cannabis. Their comment has been—using the term in a lay manner “I stopped because it makes me paranoid”, and these are people with no psychiatric illness at all other than substance misuse, so it does play a very significant part in poly-drug use.



7 April 1998]

PROFESSOR DAVID GRAHAME-SMITH,  
PROFESSOR MALCOLM LADER,  
PROFESSOR GRIFFITH EDWARDS AND  
DR MORFYDD KEEN

[Continued

*Lord Soulsby of Swaffham Prior*

43. Are the effects of multi-drug abuse additive or are there synergistic relationships between certain drugs and cannabis?

(*Professor Lader*) Well, my Lord Chairman, this is always a difficult question to answer because when you are dealing with illicit drugs in this way, you have got very little control over the way in which the drugs are being used. The laboratory work that has been done would suggest that the results are additive. There is also a problem because the effects of cannabis are sometimes prolonged and you can certainly detect it for many days and also related to the previous usage, so there is some evidence that heavy users actually get rid of cannabis rather quicker than infrequent users and this may of course explain partly their heavy use of the cannabis if they are metabolising it out of their system more quickly. I do not know of much evidence that there is any synergy, but of course it is a depressant drug, by and large, with, I would say, euphorian properties. There are many depressant drugs, both licit and illicit, which are taken from sleeping tablets to alcohol being the commonest, but the evidence would suggest that it is additive.

(*Professor Grahame-Smith*) My Lord Chairman, may I say that it is a question that interests me a very great deal from the pharmacological point of view because it is a basic principle of the way that the pharmacology of the brain works that it would not surprise me at all if one drug, let us say morphine, did not alter the way that cannabis acted simply because they react in different parts of the brain and there might be an inter-relationship, but teasing that out in a human being is an enormously difficult job, so sometimes if you think we hedge, we hedge because

our scientific knowledge of the situation is all we have.

44. There are no satisfactory animal models for looking at this aspect?

(*Professor Grahame-Smith*) I think grossly there might be, but, from the psychological point of view, probably not because it is the psychological angle that we are really interested in rather than the physical. I know that you can do psychological tests on animals, but human psychology is a very subtle thing.

*Chairman*

45. What are the long-term psychological effects of regular cannabis use?

(*Professor Grahame-Smith*) I think we have covered it and I think we may leave a copy of this paper, *Cannabis and Cognitive Functioning*, by Nadia Solowij with you because that is the latest and most comprehensive study.

(*Professor Edwards*) I would stress, my Lord Chairman, that it is as yet unpublished and I would just say that of course it should not be outside these walls for the time being, but we are very glad for you to have a copy of it, and I am sure she would want you to have a copy.

46. Well, we are most grateful to you for spending so much of your valuable time with us and answering our questions.

(*Professor Grahame-Smith*) My Lord Chairman, thank you for the occasion.



---

TUESDAY 21 APRIL 1998

---

Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.

Perry of Walton, L.  
(Chairman)  
Porter of Luddenham, L.  
Soulsby of Swaffham Prior, L.

---

**Memorandum by the British Medical Association**

1. In 1997, the British Medical Association published a report entitled *Therapeutic Uses of Cannabis* which considered the pharmacology of cannabis and cannabinoids relevant to medicinal aspects with reviews of the main therapeutic uses and adverse effects of the drug for indications such as multiple sclerosis, pain and nausea. The report also defines future research needs in this field.

2. Cannabis contains over 400 chemical compounds including more than 60 cannabinoids. Cannabinoids are derivatives of cannabis and contain compounds which constitute the active ingredients of cannabis. One particular cannabinoids, THC—delta-9-tetrahydrocannabinol—is the most potent psychoactive agent in cannabis.

3. There is considerable variation in the concentration of cannabinoids present in different preparations of cannabis.<sup>1</sup> Even if cannabis (either smoked or taken orally) from standardised preparations were shown to have therapeutic benefits, it would not be possible to know which particular agents (or combination of agents) were beneficial, and medical knowledge would not be advanced nor treatment improved. For these reasons as well as the known toxic constituents in cannabis smoke, the BMA considers that cannabis is unsuitable for medicinal use and considers only the therapeutic uses of cannabinoids in this report.

*What are the physiological effects (immediate, long term and cumulative) of taking cannabis in its various forms?*

4. Cannabinoids affect almost every body system including the cardiovascular, respiratory, immune and reproductive systems. Physiological effects may include dry mouth, poor balance, blurred vision, lack of co-ordination, muscle weakness, tremor, slurred speech, palpitation, hypotension and coughing. The main actions of cannabis in man are summarised in table three on page 19 of the BMA report.

*What are the psychological effects?*

5. The psychological effects of cannabis in man include euphoria, dysphoria, anxiety, feeling of loss of control, mental clouding, impaired memory, paranoia, hallucinations and depressions. Cannabis can also aggravate psychosis in patients with schizophrenia with a loss of control by antipsychotic drugs. It may also cause a possible precipitation of schizophrenia in vulnerable patients. These effects are also summarised in table three on page 19 of the BMA report.

*How do these effects vary with particular methods of preparation and administration?*

6. THC and other cannabinoids are rapidly absorbed on inhalation from smoked cannabis preparations. The amount absorbed depends on smoking style but may be 20–45 per cent of the THC content of a cannabis cigarette. Effects are perceptible within seconds and become fully apparent within minutes. When taken orally absorption of THC is variable and much slower. Blood concentrations reached are 25–30 per cent of those obtained by smoking the same dose, partly due to the fact that some of the THC is degraded by metabolism in the liver before reaching the circulation (first-pass metabolism). The onset of effect is delayed (0.5–2 hours) but the duration of effect may be prolonged due to continual slow absorption from the gut.

7. After smoking or intravenous administration, THC and other cannabinoids are rapidly distributed throughout the body reaching first the tissues with the highest blood flow (brain, lungs, liver, adrenals, kidney, ovaries and testes). Maximum brain concentrations are reached within 15 minutes, coinciding with the onset of maximal psychological and physiological effects. The psychological effects then reach a plateau that can last for several hours (2–4), before slowly declining. Heart rate changes decline much faster as THC leaves the blood stream and enters the brain.

8. After oral administration maximal effects occur after an hour or more but may last 5–6 hours because of continued absorption from the gut, but some psychomotor and cognitive effects persist for much longer, probably for more than 24 hours, regardless of the mode of administration.<sup>2</sup> Cannabinoids also cross the placenta, enter the foetal circulation, and penetrate into breast milk.



21 April 1998]

[Continued]

9. Cannabinoids are highly lipid soluble and accumulate in fatty tissues, from which they are only slowly released back into other body tissues and organs, including the blood stream and the brain. Because of this sequestration in fat, elimination from the body is extremely slow but although complete elimination of a single dose can take up to 30 days, the therapeutic concentration would last a much shorter time.<sup>3</sup> Clearly, with repeated dosage cannabinoids can accumulate in the body and continue to reach the brain over a longer period. Please see chapter five of the BMA report for full details on dosage and routes of administration.

*To what extent is cannabis addictive?*

10. Dependence is unlikely to present a problem with clinically prescribed doses for ill patients in therapeutic settings, but withdrawal effects may be undesirable. As well as the psychological effects (restlessness, anxiety, insomnia), there may be a rebound in intraocular pressure, nausea, diarrhoea and other physical symptoms.<sup>4</sup> Withdrawal symptoms are said to be short-lived (a few days) and mild in normal experimental subjects although they may be more severe in recreational users.<sup>5</sup> Withdrawal symptoms have not been studied in patients who use cannabis chronically for their therapeutic effects.

11. Experience with patients receiving opioids for pain relief shows that therapeutic use rarely leads to misuse.<sup>6</sup>

*To what extent do users develop tolerance to cannabis?*

12. Tolerance has been shown to develop to many effects of cannabis in normal subjects. These include effects on mood, heart rate, blood pressure, salivary flow, intraocular pressure, EEG changes and psychomotor performance<sup>7</sup> and anti-emetic effects. Such tolerance can develop within weeks with repeated dosage though not at the same rate or degree for different effects.<sup>8</sup> Tolerance can be an advantage in decreasing unwanted effects (eg, dry mouth, dysphoria) but a disadvantage if a desired effect (eg, decreased intraocular pressure) is involved. Further research is needed to determine whether tolerance can be overcome by raising the dose.

*What is the evidence that cannabis in its various forms has valuable medicinal actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?*

13. Chapter 3 of the BMA report considers in detail the potential therapeutic uses of cannabis for several indications including:

- nausea and vomiting associated with cancer chemotherapy
- muscle spasticity
- pain
- anorexia (loss of appetite)
- epilepsy
- glaucoma
- bronchial asthma
- mood disorders, psychiatric conditions
- hypertension

For each indication, the existing pharmacological treatments are considered, along with the potential effects of cannabis and cannabinoids, the research needed and the conclusions.

14. In summary, these are:

*Anti-emetics:* Further research is needed on the use of delta-8-THC as an anti-emetic, the use of cannabidiol in combination with THC, and the relative effectiveness of cannabinoids compared with 5-HT<sub>3</sub> antagonists. Further research is needed in other cases of nausea and vomiting such as post-operative.

*MS, spinal cord injury and other spastic disorders:* A high priority should be given to carefully controlled trials of cannabinoids in patients with chronic spastic disorders which have not responded to other drugs which are indicated. In the meantime, there is a case for the extension of the indications for Nabilone and THC for use in chronic spastic disorders unresponsive to standard drugs.

*Pain:* The prescription of Nabilone, THC and other cannabinoids (including the new more selective synthetic agents such as levonantradol, (–)-HU-210 and others in the process of development) should be permitted for patients with intractable pain. Further research is needed into the potential of cannabidiol as an analgesic in chronic, terminal and post-operative pain.



21 April 1998]

[Continued]

*Epilepsy:* Trials with cannabidiol (which is non-psychoactive) used to enhance the activity of other drugs in cases not well controlled by other anticonvulsants are needed.

*Glaucoma, asthma:* Cannabinoids at present do not look promising for these indications, but much further basic and clinical research is needed to develop and investigate cannabinoids which lower intra ocular pressure, preferably by topical application (eg eye drops, inhalant aerosols), without producing unacceptable systemic and central nervous system effects.

*Stroke and neuro-degenerative disorders:* The potential of (+)-HU-210 for these indications should be explored through further research.

*Immunological effects:* Further research is needed to establish the suitability of cannabinoids for immunocompromised patients, such as those undergoing cancer chemotherapy or those with HIV/AIDS.

Please refer to chapter three of the BMA report for full details.

*How strong is the scientific evidence in favour of permitting medical use?*

15. Arguments in favour of sanctioning cannabis for medical use have been based mainly on anecdotal reports.<sup>9</sup> Although many of these may be convincing, they do not by themselves constitute scientific evidence.<sup>10</sup> On the other hand, the accumulation of scientific evidence has been hampered by regulations restricting the use of cannabinoids to one clinical indication (Nabilone and Dronabinol in the UK and Dronabinol in the US as anti-emetics in cancer chemotherapy).

16. It can be concluded that although cannabis itself is unsuitable for medical use, individual cannabinoids have a therapeutic potential in a number of medical conditions in which present drugs or other treatments are not fully adequate. Long-term effects of chronically administered cannabinoids have not been studied, but present evidence indicates that they are remarkably safe drugs with a side-effects profile superior to many drugs used for the same indications.

*How strong is the scientific evidence in favour of maintaining prohibition of recreational use?*

17. Studies have shown that cannabis can have actions on many body systems and, like all drugs can cause unwanted effects. Acute effects can include sedation, psychological effects (see question 2), physiological effects (see question 1), impairment of psychomotor and cognitive performance (see page 66 of BMA report), endocrine effects and immunosuppressant effects (see page 68). There are also particular hazards associated with smoking cannabis as the smoke from herbal cannabis contains all the toxic constituents of cigarette smoke (apart from nicotine) plus also greater concentrations of benzantracenes and benzpyrenes (both carcinogens) than tobacco smoke. It has been estimated that smoking a cannabis cigarette (containing only herbal cannabis) results in an approximately five-fold greater increase in carboxyhaemoglobin concentration, a three-fold greater increase in the amount of tar inhaled, and a retention in the respiratory tract of one third more tar than smoking a tobacco cigarette.<sup>11</sup> Thus chronic cannabis smoking, like tobacco smoking, increases the risk of cardiovascular disease, bronchitis, emphysema and probably carcinomas of the lung and aerodigestive tract.

18. Since the publication of the report, the BMA has been involved in several meetings on this subject including a meeting with the Chief Medical Officer at the Department of Health in March 1998 to discuss likely further actions in moving forward clinical trials of cannabinoids for therapeutic uses. At the meeting, it was agreed that an appropriate body to conduct such trials was required and that it should be an independent or institutional research organisation. The Clinical Cannabinoids Group (CCG) at the University of Aberdeen was identified as perhaps being best placed to do this. The membership of the group includes those planning to set up trials of cannabinoids who will provide expertise advice and knowledge to clinical researchers to facilitate such research. The Royal Pharmaceutical Society of Great Britain provide the secretariat support for this group. The group have been approached with this suggestion.

#### REFERENCES

1. Gough T. (1991) *The Analysis of Drugs of Abuse*. Chichester: John Wiley and Sons
2. Leirer VO, Yesavage JA, Morrow DG. (1991) *Aviation Space and Environmental Medicine*; 62:221–227
3. Maykut MO. (1985) Health consequences of acute and chronic marijuana use. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*; 9:209–238
4. Jones RT, Benowitz N, Bachman J. (1976) Clinical studies of cannabis tolerance and dependence. In: *Chronic Cannabis Use* (ed Dornbush RL, Freedman AM, Fink M). pp 221–239, New York: New York Academy of Sciences
5. Stephens RS, Roffman RA, Simpson EE. (1993) Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology*. 61;1100–1104



21 April 1998]

[Continued

6. Twycross RG, McQuay HJ. (1989) Opioids. In: *Textbook of Pain* (eds Wall PD, Melzack R). 2nd edition, pp 686–701. London : Churchill Livingstone
7. Jones RT, Benowitz N, Bachman J. (1976) Clinical studies of cannabis tolerance and dependence. In: *Chronic Cannabis Use* (Ed Dornbush RL, Freedman AM, Fink M). pp 221–239, New York: New York Academy of Sciences
8. Pertwee RG. (1991) Tolerance to and dependence on psychotropic cannabinoids. In: *The Biological Bases of Drug Tolerance and Dependence* (ed Pratt JA). pp 231–263, London: Academic Press
9. Grinspoon L, Bakalar JB. (1993) *Marihuana, the Forbidden Medicine*. New Haven and London: Yale University Press
10. Hall W, Solowij N, Lemon J (eds). (1994) *The Health and Psychological Consequences of Cannabis Use*. National Drug Strategy Monograph Series No. 25, Canberra, Australian Government Publishing Service
11. Benson M, Bentley AM. (1995) Lung disease induced by drug addiction. *Thorax*; 50:1125–1127

3 April 1998

### Memorandum by Professor Heather Ashton

#### 1. INCREASED POTENCY OF CANNABIS PREPARATIONS

1.1 Preparations of cannabis that are used today in the UK are about 10 times more potent than those taken in the “flower power” days of the 1960s and 1970s. For example, a typical 1970s “reefer” contained about 10mg of tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis, while a typical “joint” today may contain 60-150mg or more of THC (Table 1). This increase in potency results from sophisticated plant breeding and cultivation methods leading to highly potent varieties of cannabis such as Skunkweed.

1.2 The increase in potency is important because the physical and psychological effects of cannabinoids (THC and others) are dose-related: the bigger the dose the greater the effect. Most of the research on cannabis was carried out in the 1970s using relatively small doses, and much of that research is obsolete today. The acute and long-term effects of the present high dose use of cannabis have not been systematically studied.

#### 2. DOSES OF CANNABINOIDS OBTAINED FROM DIFFERENT MODES OF ADMINISTRATION

2.1 The dose of cannabinoids received varies with the mode of administration. With smoking from cannabis cigarettes or pipes, about 50 per cent of the THC present in the preparation is absorbed and enters the bloodstream. When taken by mouth (baked into food) about 15 per cent of the THC enters the bloodstream. An increasingly common practice in some parts of the UK is to inhale the smoke from “buckets”. The cannabis preparation is placed in a sawn-off plastic bottle and ignited, and the resulting smoke and fumes inhaled. The proportion of cannabis absorbed from this method is unknown (probably very high).

2.2 It is clear that whatever the method of administration, a present-day cannabis user can easily obtain a dose of THC far in excess of the 2.5-5mg which have been shown in earlier studies to be sufficient to produce intoxication and many physical effects (eg Maykut 1985; Ashton et al 1981 and many others). There is no evidence that recreational cannabis users moderate their smoking style in order to limit or “titrate” the dosage taken from potent preparations (although there are no systematic studies). Evidence from blood tests in drivers on the continent shows that many users do in fact take very high doses, often several 100mg of THC (Daldrup and Musshof 1993).

#### 3. SLOW ELIMINATION OF CANNABINOIDS

3.1 The distribution of THC in the body following a single dose is shown in Fig 1. Once absorbed, the cannabinoid rapidly enters the brain and the onset of psychological effects is within 15 minutes of smoking. THC then leaves the brain more slowly, which is why psychological “high” lasts two to four hours. Meanwhile the THC enters other tissues of the body, finally accumulating in fatty tissues and reaching maximum concentrations about four days after administration. THC is very fat soluble and is extremely slowly released from fatty tissues, from which it re-enters the blood and recirculates to other tissues including the brain. THC is finally metabolised by the liver, but complete elimination of a single dose from the body takes up to 30 days.

3.2 It is clear that with repeated dosage, high concentrations of cannabinoids can build up in the body and exert continuing effects. A considerable percentage of cannabis users take the drug weekly or more frequently (eg 20 per cent of university students; Webb et al 1996) and must therefore accumulate cannabinoids. This slow elimination of cannabinoids and accumulation in tissues is important because it has implications for performance in complex tasks such as car driving and aircraft piloting (see below).



21 April 1998]

[Continued

#### 4. SITES OF ACTION OF CANNABINOIDS IN THE BRAIN AND BRAIN FUNCTIONS AFFECTED

4.1 THC is concentrated in certain areas of the brain where it exerts its effects by acting on specific receptors. Brain sites particularly affected are shown in Table 2. They include areas involved in logical thought, reasoning, judgement and memory; areas involved in sensory perception and motor coordination, and areas involved in the genesis of emotions, including that of pleasure. As a result, cannabis exerts many psychological and physical actions and can impair performance in a number of everyday activities.

#### 5. IMPAIRMENT OF PERFORMANCE BY CANNABIS

The most marked effects of cannabis on performance are on complex tasks which require attention to several events at once ("divided attention tasks").

5.1 *Effects on motor car driving.* A large number of investigations have shown that cannabis, even in small doses (5-10mg THC in a cannabis cigarette) impairs car driving skills. The results are summarised by Nahas (1984) and the types of impairments found are shown in Table 3.

5.2 *Road traffic accidents.* In many countries, including the UK, cannabis is the most common drug, apart from alcohol, to be detected in individuals involved in traffic accidents. A survey from the Department of the Environment, Transport and the Regions (DETR 1998) found that 10 per cent of drivers involved in fatal accidents tested positive for cannabis post mortem (Table 4). (Eighty per cent of these did not have alcohol above the legal limit.) Cannabis was detected in 38 per cent of impaired drivers in the US (National Highway Traffic Safety Administration, 1992) and similar results have been reported in Australia, Canada, and several European countries.

5.3 *Effects on aircraft piloting skills.* Cannabis has been shown to cause serious impairment of aircraft piloting skills in experienced pilots performing flight simulator tasks. The results of one of several studies (Fig 1) showed that performance decrements persisted for up to 48 hours after a single cannabis cigarette containing 20mg THC. After 24 hours the pilots were unaware that their performance was affected.

5.4 *Railroad and other accidents.* Cannabis has been implicated in major railroad accidents (Nahas 1993) and it is likely that cannabis-related risks can be also apply to train drivers, signal operators, air-traffic controllers, operators of complex machinery, and many other skilled activities not enumerated here.

5.5 *Implications.* These results suggest that cannabis use poses a public safety hazard with risks of injury to others. However, because of the slow elimination of cannabis (3.1), it is not possible from blood, urine, saliva or sweat tests to relate detected cannabinoid concentrations to the degree of intoxication of a driver, or machine operator at the time of an incident, or to prove that cannabis was the cause of an accident.

#### 6. TOLERANCE AND WITHDRAWAL EFFECTS

6.1 Tolerance to many psychological and physical effects of cannabis has been demonstrated conclusively in man (Table 5a). It develops rapidly, ie after 10 days of repeated daily use. Tolerance to some of the performance impairments occurs, but the degree is limited and performance after taking cannabis may still be worse than in the drug-free state. Tolerance to the recreational "high" encourages escalation of dosage.

6.2 Withdrawal effects of cessation of cannabis use have also been demonstrated conclusively in man (Table 5b). A daily dose of 180 mg THC (one or two modern joints) for 11-21 days is sufficient to produce a well-defined withdrawal syndrome (Jones 1983). Symptoms are similar to the withdrawal symptoms of alcohol, tranquillisers and opiates. They start about 12 hours after the last dose of cannabis and are immediately relieved by a further dose, thus encouraging continued use.

#### 7. DEPENDENCE AND ADDICTION

7.1 Development of withdrawal effects is evidence of a degree of physical dependence. Recent animal work (Tanda et al 1997), has shown that THC activates precisely the same specific "reward" areas in the brain and releases the same chemicals in similar amounts as cocaine, heroin, amphetamine, and alcohol. This effect is believed to be the basic common action of all drugs that produce a recreational "high" and cause drug dependence in man. This action is in all likelihood the basis of cannabis' recreational use (people take it for "pleasure"; Webb et al 1996) and is strong evidence that cannabis is at least potentially addictive.

7.2 An increasing number of people who feel themselves to be dependent on cannabis are seeking professional help with withdrawal (North East Council for Addictions; Student Counselling Service, Newcastle University). Similar experience is reported from Australia, New Zealand and the US.



21 April 1998]

[Continued

## 8. LONG-TERM COGNITIVE EFFECTS OF CANNABIS

8.1 There is no clear evidence concerning long-term effects of cannabis use on cognitive performance. However, investigations have shown that impairments of memory persist six weeks after cessation of daily cannabis use in adolescents (Schwartz 1991), and attentional deficits may persist two years after cessation of use in long-term (three to four years) regular cannabis users (Solowij 1995).

8.2 This question requires further investigation since cannabis use in the UK often starts at school (Miller and Plant 1996) and continues into young adulthood (Webb et al 1996), with the result that a considerable number of people in this country use cannabis recreationally for several years.

## 9. RESPIRATORY AND CARDIOVASCULAR HEALTH RISKS FROM CANNABIS SMOKING

9.1 The smoke from a cannabis cigarette contains all the same constituents (apart from nicotine) as tobacco smoke, including carbon monoxide, irritants and carcinogens, some of which are in greater concentration than in tobacco smoke. Because of the way in which it is smoked, a single cannabis joint delivers the equivalent in carbon monoxide, irritants and carcinogens of four to five tobacco cigarettes and carries similar cardiovascular and respiratory health risks including the risk of lung cancer (Benson and Bentley 1995; Wu et al 1998).

9.2 No long-term prospective studies have been carried out, but the effects of cannabis are probably cumulative, depending on the amount of exposure. Any increased incidence of cardiovascular and respiratory health problems resulting from the recent rise in prevalence of cannabis use among young people will only become apparent after a latent period of 10 to 20 years.

## 10. MENTAL HEALTH RISKS OF CANNABIS USE

10.1 Cannabis intoxication can precipitate severe psychiatric reactions including paranoia, mania, and schizophrenic-like states with persecutory or religious delusions. These reactions appear to be becoming more common with potent preparations such as Skunkweed (Table 21), may last for weeks and can occur in people with no previous psychiatric history (McGuire et al 1994).

10.2 In addition, cannabis can aggravate or precipitate schizophrenia in vulnerable individuals and may antagonise the therapeutic effects of antipsychotic drugs in previously well-controlled schizophrenic patients.

10.3 These effects are important in the context of increasing numbers of mentally ill patients in community care and the high risks of cannabis use (probably over 40 per cent, Menezes et al 1996) in psychiatric patients.

## CONCLUSIONS

11.1 The above considerations (and others contained in my comprehensive review for the Department of Health, Ashton, March 1996) constitute strong scientific evidence in favour of maintaining prohibition of recreational use of cannabis.

11.2 Scientific evidence in favour of permitting medical use of individual pure and synthetic cannabinoids (but not cannabis itself) is contained in the British Medical Association report (BMA 1997) to which I was a major contributor.

## REFERENCES

- Ashton H, Golding J, Marsh V R, Millman, J E, Thompson J W (1981). *Br J Pharmacol* 12: 705–720.
- Ashton C H (1996). Report for Department of Health.
- Benson M and Bentley A M (1995). *Thorax* 50: 1125–1127.
- Daldrup T and Musshoff F (1993). *Alcohol, Drugs and Traffic Safety* (Eds. Utzelmann, Berghaus, Kroj) Verlag TUV Rheinland GmbH, Koln pp 497–504.
- DETR (1998). Report on incidence of drugs in road accidents victims: interim results of survey, January 1998.
- Jones R T (1983). *Cannabis and Health Hazards* (Eds K O Fehr, H Kalant). Toronto Addiction Research Foundation.
- Jones R T, Benowitz N, Bachman, J (1976). *Chronic Cannabis Use* (Eds R L Dornbush A M Freedman, M Fink). New York Academy of Sciences pp 221–239.
- Leirer V O, Yesavage J A, Morrow D G (1991). *Aviat. Space Environ. Med.* 60: 1145–52.
- Maykut A J (1985). *Prog Neuropsychopharmacol. Biol Psychiatry* 9: 209–238.



21 April 1998]

[Continued

McGuire P K, Jones P, Harvey I, Bebbington P, Toone B, Lewis S, Murray R M (1994) *Schizophrenia Research* 13: 161–7.

Menezes P R, Johnson S, Thornicroft G, et al (1996). *Br J Psychiat.* 168: 612.

Miller P MNCC., and Plant M (1996). *BMJ* 313: 394–7.

Nahas G G (1975). *Medical Aspects of Drug Abuse* (Ed R W Richter) Harper & Row, Maryland pp 16–36.

Nahas G G (1984). *Marihuana in Science and Medicine* (Ed G G Nahas) Raven Press, New York, pp 16–36.

Nahas G G (1993). *Cannabis: Physiopathology, Epidemiology, Detection* (Eds G G Nahas, C Latour. CRC Press.

National Highway Traffic Safety Administration (1992). Report No DOT HS 808 058.

North East Council for Addictions (personal communication).

Schwartz R H, (1991). *Physiopathology of Illicit Drugs: Cannabis, Cocaine, Opiates* (Eds G G Nahas and C Latour). Advances in Biosciences Vol 80, Pergamon Press pp 13–21.

Solowij N (1995) *Life Sciences* 56: 2119–26.

Student Counselling Service, Newcastle University (personal communication).

Tanda G, Pontieri F E, Di Chiara G (1997) *Science* 276: 2048–50.

Webb E, Ashton C H, Kelly P, Kamali F (1996) *Lancet* 348: 922–5.

Wu T-C, Tashkin D P, Djahed B, Rose J E (1988). *New Engl J Med* 318: 347–51.

Table 1

## PREPARATIONS OF CANNABIS (U.S. AND U.K.)

| Form                  | Source  | THC content (this is extremely variable and the figures are approximate) |
|-----------------------|---|--|
| Marijuana (U.S.)      | dried leaves/stalks/flowers/seeds   |  |
| Cannabis (U.K.)       | traditional cigarette (reefer) of 1960s and 1970s   | 1-3% THC (~10mg/reefer)  |
| (Herbal cannabis)     | modern cigarette (joint) of 1980s–90s result of intensive cultivation and more potent subspecies (sinsemilla, “skunkweed”, “Silver Pearl” and others) |  |
| Hashish (U.S.)        | resin secreted by plant   |  |
| Cannabis resin (U.K.) | bricks, cakes, slabs  | 10-20% THC   |
| Hashish oil           | product of extraction by organic solvents   | 15-30% THC (sometimes up to 65%)   |

Table 2

## BRAIN AREAS AND FUNCTIONS AFFECTED BY CANNABINOIDS

| Brain area      | Functions   |
|-----------------|---|
| Cerebral cortex | — logical thought, reasoning, judgment                  |
| Hippocampus     | — memory functions, time appreciation                   |
| Limbic system   | — pleasure/reward centres, emotions                     |
| Sensory areas   | — perception of sound, colour etc.                      |
| Motor areas     | — muscle coordination, balance, psychomotor performance |

Table 3

## CANNABIS EFFECTS LIKELY TO IMPAIR DRIVING AND PILOTING SKILLS

|  |   |
|--|---|
| Slowed complex reaction time               | Impaired short-term memory                        |
| Poor detection of peripheral light stimuli | Impaired attention                                |
| Poor oculomotor tracking                   | Inability to carry out complex or demanding tasks |
| Impaired coordination                      | Poor judgment                                     |
| Size and time distortion                   | Additive effects with alcohol and other drugs     |
| Increasing risk taking                     |   |

21 April 1998]

[Continued

Table 4

PERCENTAGE OF VARIOUS ROAD USER GROUPS TESTING POSITIVE FOR MEDICINAL AND ILLICIT DRUGS (SURVEY OF 619 ROAD USER FATALITIES IN THE UK)

| (Number)                       | % testing positive |                 |                     |                     |                |
|--------------------------------|--------------------|-----------------|---------------------|---------------------|----------------|
|                                | Drivers<br>(284)   | Riders<br>(125) | Passengers<br>(126) | Pedestrians<br>(84) | Total<br>(619) |
| Medicinal Drugs                | 4                  | 6               | 9                   | 8                   | 6              |
| Illicit drugs:                 | 18                 | 14              | 21                  | 8                   | 16             |
| Cannabis                       | 10                 | 5               | 13                  | 1                   | 8              |
| Amphetamines                   | 2                  | 2               | 2                   | 2                   | 2              |
| Opiates                        | 1                  | 1               | 2                   | 1                   | 1              |
| Cocaine                        | 0                  | 0               | 0                   | 0                   | 0              |
| Methadone                      | 1                  | 0               | 0                   | 0                   | 0              |
| Multiple drugs                 | 4                  | 6               | 4                   | 4                   | 5              |
| Alcohol (over the legal limit) | 22                 | 15              | 29                  | 31                  | 23             |

Source: DETR (1998)

Table 5a

CANNABIS ACTIONS TO WHICH TOLERANCE HAS BEEN SHOWN TO DEVELOP

|                                      |                                  |
|--------------------------------------|----------------------------------|
| Mood changes                         | EEG slowing (slower brain waves) |
| Tachycardia (increased heart rate)   | EEG evoked potential alterations |
| Hypotension (fall in blood pressure) | Sleep EEG changes                |
| Skin temperature decrease            | Sleep time and quality           |
| Body temperature increase            | Eye tracking impairment          |
| Salivary flow decrease               | Psychomotor task performance     |
| Intraocular pressure decrease        | Behavioural changes              |

(EEG = electroencephalography)

Source: Jones et al. (1976)

Table 5b

SIGNS AND SYMPTOMS OF ABSTINENCE AFTER ABRUPT CESSATION OF ORAL CANNABIS (210 mg THC/day for 11-21 days)

|                    |                                |
|--------------------|--------------------------------|
| Mood changes       | Hyperactivity                  |
| Disturbed sleep    | Hiccups (rare)                 |
| Decreased appetite | Nasal congestion (rare)        |
| Restlessness       | Weight loss                    |
| Irritability       | Hemoconcentration              |
| Perspiration       | Salivation                     |
| Chills             | Tremor                         |
| Feverish feeling   | Loose bowel movements          |
| Nausea             | Body temperature increase      |
| Abdominal distress | Sleep EEG eye movement rebound |
| Tremulousness      | Waking EEG changes             |
|                    | Intraocular pressure increase  |

(Cannabis replaced with placebo under double blind conditions)

Source: Jones et al. (1976)



21 April 1998]

[Continued

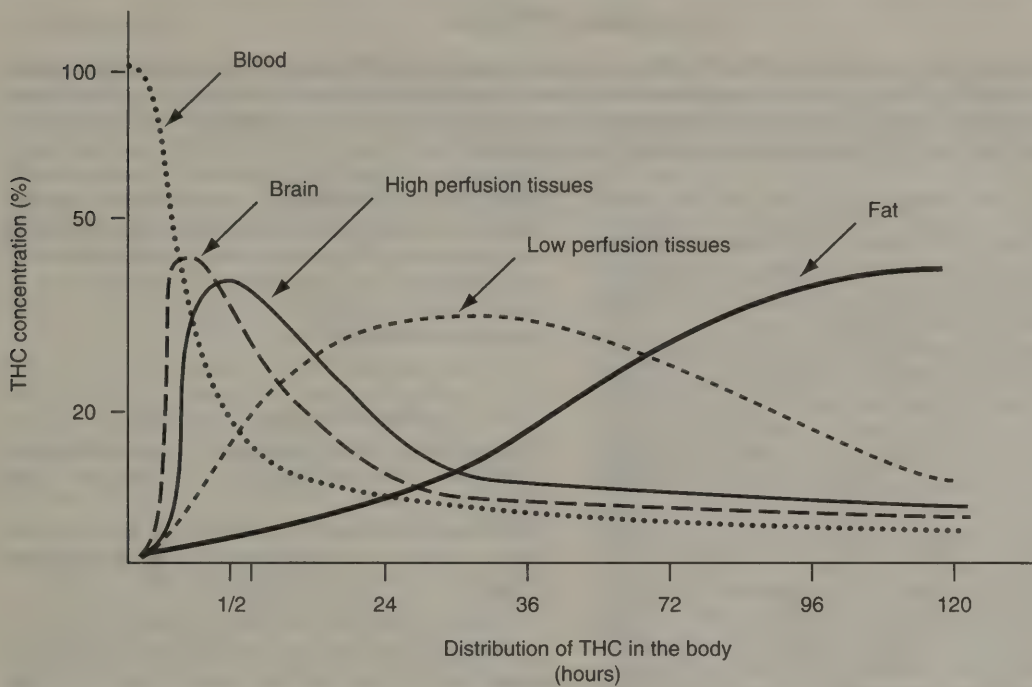


Fig. 1 Distribution of THC in the body

The distribution of THC after a single administration in plasma and body tissues. Note the "biphasic" disappearance in plasma. The rapid phase (in minutes) indicates a rapid uptake of the drug by fat containing tissues. The slow phase (in days) shows the release of THC by these tissues. (Nahas, 1975)

#### Pilot Performance Decrement Scores

Squares & dashes = 20 mg dose, Circles & solid line = Placebo

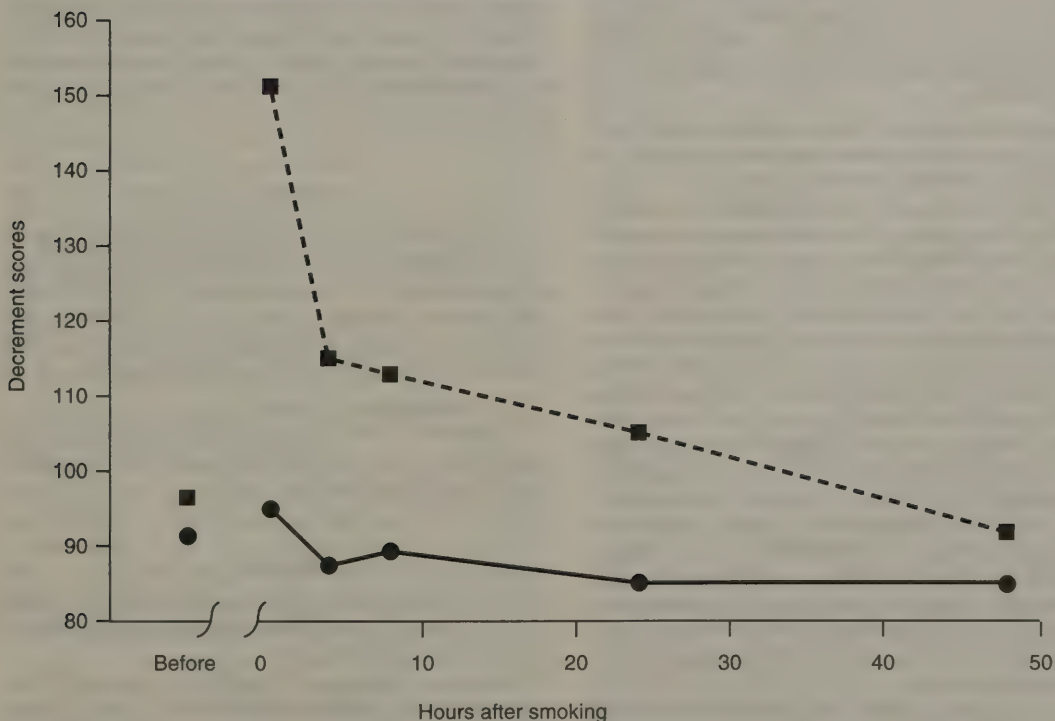


Fig. 2 Effect of smoking a cannabis cigarette containing 20mg THC on pilot performance in a flight simulator landing task. (Leirer et al, 1991)

5 April 1998

21 April 1998]

[Continued]

### Examination of Witnesses

PROFESSOR VIVIENNE NATHANSON, Head of Professional Resources and Research Group, British Medical Association (BMA), and PROFESSOR HEATHER ASHTON, Emeritus Professor of Clinical Psychopharmacology, University of Newcastle-upon-Tyne, and consultant writer for the BMA report *Therapeutic uses of Cannabis*, were called in and examined.

#### Chairman

47. Professors Nathanson and Ashton, thank you for coming. Before we begin, perhaps you would introduce yourselves and explain why the BMA became involved in this matter.

(*Professor Nathanson*) My Lord Chairman, we are very grateful for the opportunity to present evidence. I am Vivienne Nathanson, head of the professional work of the British Medical Association, which includes its work on science, ethics and health policy. With me is Professor Heather Ashton, emeritus professor of clinical psychopharmacology at the University of Newcastle-upon-Tyne who as the BMA representative is a major contributor to the report. She has also submitted independent evidence on some other issues. The BMA became involved because its members said that some patients had said that they had been using herbal cannabis and getting relief from the symptoms of certain medical conditions. As doctors, members wanted to know whether there was any evidence of this and, if so, what it was and whether there were alternatives. We wrote the report based on the evidence particularly on the use of cannabinoids worldwide. As far as we are concerned, it is important to stress the difference between the cannabinoids and herbal cannabis. It is necessary to emphasise the many different effects that are likely to be found among the 400 or more active ingredients of cannabis and the opportunity to look at cannabinoids, either natural or synthetic, which can be single drugs hopefully with predictable effects and side-effects.

48. Can you summarise for us in what therapeutic situations cannabis appears to be preferable to treatments that are currently licensed?

(*Professor Nathanson*) At the moment, we do not believe that there are any situations in which it can be said that it is preferable to existing treatments. But there are some circumstances in which there is evidence that cannabinoids may work either with existing medical treatments as an adjunct or as an alternative if those treatments have failed. However, so far I do not think that there are any such drugs available which we would regard as a first line treatment. Perhaps the two largest areas in which there is some evidence of good therapeutic potential, as an adjunct to treatment, is the treatment of chronic pain and muscle spasm. That is, in addition to chemotherapy, particularly anti-cancer chemotherapy. There are lots of other areas in which cannabinoids are active and may have therapeutic potential, but I do not believe that so far there is any evidence to support the view that they are preferable to existing treatments.

(*Professor Ashton*) I agree with that. One is talking here about cannabinoids, not cannabis. They may be used in certain conditions which have not responded to standard drugs or where the side-effects of standard drugs are unacceptable, for example people who are distressed by illnesses such as multiple sclerosis. They may be most valuable as adjuncts to

existing treatment, but we simply do not have the evidence to demonstrate it. In the whole world there have been only 41 patients with multiple sclerosis who have undergone controlled clinical trials of cannabinoids or cannabis. We do not know, so there is a need for research.

#### Lord Porter of Luddenham

49. Professor Ashton, you said "cannabinoids, not cannabis". In what context do you draw that distinction?

(*Professor Ashton*) We are making a distinction between using individual cannabinoids for medical purposes as opposed to herbal cannabis.

50. What conclusion do you draw from that?

(*Professor Ashton*) I am talking about the use of cannabinoids for medical uses. Most of the controlled trials have been done with pure cannabinoids.

51. But the distinction is between those that have been the subject of trials and those that have not. When you refer to one and not the other are you distinguishing between them because one has been tried and not the other, or because one is preferable to the other?

(*Professor Ashton*) Both. The only controlled trials have been done with single cannabinoids. We think that that is preferable because at least we know which cannabinoid we are working with as opposed to the 60 cannabinoids and a lot of other substances in the whole of the plant.

#### Lord Butterfield

52. Presumably, another reason is that it was easier to use placebos in the 40 cases that were the subject of trials rather than the smoked form of cannabis?

(*Professor Ashton*) Years ago I carried out experiments myself. One can use ordinary herbal cigarettes that are cannabis and nicotine-free.

53. Are they good enough?

(*Professor Ashton*) They worked with our students some years ago. Some claimed to get quite a good "high" from placebo cigarettes.

#### Chairman

54. We understand that cannabis was widely used in the previous century. In what situations was it used, and why did it stop?

(*Professor Nathanson*) It was used in many of the same kinds of conditions that we are talking about today. Certainly, it was used for pain and muscle spasm. It was used as an anti-emetic and also as a sedative and hypnotic. Predominantly, it was used as a tincture, or alcohol-based fluid, and it fell out of use simply because newer drugs came along which were more predictable and had other routes of



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued

Chairman *contd.*]

administration. In particular, at the same time hypodermic syringes were developed which provided a good route of administration for some of the new drugs that became available for conditions that were difficult to treat. Therefore, it fell out of use because it did not have a therapeutic profile that doctors found helpful in the treatment of the majority of their patients.

*Lord Porter of Luddenham*

55. The BMA report says that herbal cannabis is unsuitable for medical use largely because of the difficulty of achieving a standard dose, the hazards of smoking, the possibility of adulteration and so forth. Yet the report acknowledges that significant numbers of people use herbal cannabis to relieve the symptoms of MS. Would you advise those people to stop it for their own good?

(*Professor Nathanson*) Yes and no. In an ideal world, if there were perfect treatments one would tell people to stop because the risks of smoking herbal cannabis, given the fact that it contains 400 active ingredients, are significant. As more trials became available using either pure derivatives or synthetic cannabinoids, we would suggest to doctors that their patients might be considered as candidates for those trials. These are exactly the patients in whom we want to try to produce the beneficial effects, perhaps without some of the side-effects. Having said that, we also recognise that there are not many trials going on at the moment. Some trials may take time to establish. Those patients who are using these herbal preparations need to be aware of the risks and when alternatives are available. It is also important that patients go back to their doctors and ask whether alternatives are available. The development in medical therapeutics is considerable. Repeatedly, we find that, sadly, patients do not come forward to have their medication changed because it does not have quite the positive effect that it may have when there are other new prescribable drugs on the market. Having said that, if a patient is getting a benefit, he is not suitable for a trial, he has talked to his doctor and there are no alternatives available, we believe that he should be treated sympathetically in terms of the law and any penalty that may be imposed for the use of herbal cannabis for the relief of symptoms.

56. Do you accept that there are cases where there is no alternative treatment?

(*Professor Nathanson*) We accept that there are many patients who gain some benefit and who may not gain the same benefit from existing medical treatments. These are all anecdotal reports. That is why it is important to have good research to try to isolate the beneficial effects and deliver them from a measurable and controllable drug.

*Lord Dixon-Smith*

57. Is there not a problem here in that even if one gets the research funded to produce the results drug companies who produce pure substances which are pharmaceutically certain in their consequences will always face an evil competitive influence? A person can go out on to the street and buy the weed at a very

low price. Therefore, I believe that manufacture of the drug will be very difficult to get under way. Are we not dealing with what may be termed relative evils? Has work been done on the relative ill-effects, of the use of cannabis in this situation, the effects of disease and the use of other substances which can have equally damaging effects, if they are persisted in for too long?

(*Professor Nathanson*) That question contains a number of issues. First, we must ensure that we look at what we are trying to achieve with cannabinoids. As with any other medical drug, the ideal is a desired medical effect, whether it be pain relief or reduction of muscle spasm, without unwanted side-effects. Unwanted side-effects may include changes in blood pressure, raised pressure in the eyes or all kinds of different things. They may include the psychoactive effects that one gets from cannabis and many of the cannabinoids but not all. It is extremely important to recognise that in trying to reduce the relief of symptoms for someone with a chronic condition, such as multiple sclerosis, one does so in such a way that improves the person's general quality of life. If we can relieve the symptom of, say, muscle spasm without clouding awareness or making it difficult for the person to do something like driving then it may bring enormous benefits over and above the effects that currently may or may not be produced by other therapies. We have to aim for the therapeutic option. Secondly, we are dealing with many medical conditions that are chronic with which people may live for many years. Perhaps that will increase the length of time during which people live with these conditions. We have to think of side effects. Herbal cannabis, as with any other drug—in this case, many drugs together—has side-effects, which is inevitable. All drugs have side-effects. There must be research done on that because it is part of the balance of benefit and effect for the individual patient. In looking for purer compounds the aim is to be better able to predict the side-effects and their likelihood in individual patients and to warn them. It is possible for a doctor to decide, as with any other drug, the balance of advantage to the particular patient of using this particular drug as against another. The cost is interesting. When one looks at drugs, clearly to develop a drug from scratch where one has no idea which system of the body is to be targeted to produce a desired effect—say, the reduction in blood pressure, which can be achieved in many different ways—the costs can be enormous. But with cannabinoids one knows a considerable amount about the chemistry and the body receptors. A great deal of computer modelling can be done in developing synthetics. We should also recognise that the number of patients who may benefit in a worldwide context may be very considerable. For example, around the world there are large numbers of people with muscle spasm resulting from spinal injuries, as well as chronic diseases or birth damage. I do not believe it is impossible for a synthetic cannabinoid to be developed to produce the desired effect and to be marketed at a price that makes it widely available, not just in those countries which spend a considerable amount of money on health. I do not think that we should therefore be put off this research, because the benefits to patients of



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Lord Dixon-Smith *contd.*]

producing single agents or agents which with two or three compounds work synergistically one with the other can be enormous—much more so than using the uncertain natural substance.

(*Professor Ashton*) I agree with that. It was suggested that drug companies might be in competition with herbal cannabis. I think that the companies would be very keen to do research and develop drugs which had an impact on common diseases like multiple sclerosis. Another big drawback of smoked herbal cannabis which has not been fully appreciated, even by MS sufferers who use it, is the risk of passive smoking. There is now evidence from America that cannabinoids have been found in the blood of children in families where cannabis is smoked. They also get all the smoke constituents. You will be aware of the debate about passive tobacco smoking and the risks of that. The risks would be the same here. People will be using this long term, if it is for multiple sclerosis which does not shorten life. They will probably have to use it frequently. Although the mental effects last for a long time, the physical effects are much more short-lived. They will be taking it at least twice a day. Therefore, there is a risk, not only to the individual patient. Another factor to bear in mind is that research into individual cannabinoids is more likely to be fruitful than research into the whole plant.

Chairman

58. In the 1970s some of the pharmaceutical companies made a number of attempts to produce synthetic cannabinoids which did not have the psychological effect or “high”. That failed. None of them managed to separate that effect.

(*Professor Ashton*) That was true in the ‘seventies. However, since then science has made big advances in localising receptors and endogenous substances in the body which act like cannabis. We are now in a much better position to isolate the various effects. Cannabis affects almost every system of the body probably at different sites in the brain. It may well be possible to separate some of them, although we may find that the “high” is an integral part of what makes a person suffering from multiple sclerosis feel better.

Lord Butterfield

59. Can you see any way whereby we can tag people who are smoking cannabis so that when they die their death certificates can be studied to see if they have developed cancer of the lung? Ten years ago I did a study involving about 10,000 people and I was allowed to tag those people to see what happened to them later. Do you see any way in which that can be done for cannabis smokers who may volunteer to have their notification of death tagged in order to unravel it? If it is a real hazard it will emerge early on rather than waiting for somebody to find an excuse for doing it. Have you any ideas?

(*Professor Ashton*) That is a very interesting question. Do you mean a physical tag like a radioactive substance?

60. No. It is a device whereby the registrar of birth, deaths and marriages has death certificates of a

certain sub-group of the population drawn to his attention. I think that it cost £2.50 per person. The problem is that the individual must give permission. If permission is given the men in blue will regard it as a marvellous way of collaring a lot of people who are illegitimately smoking marijuana. For example, perhaps a person suffering from multiple sclerosis who gets a benefit from using this drug will allow himself or herself to be identified so that the relevant information is available at death. This seems to me to be an important aspect, particularly when it is pointed out that a joint has four to five times as much carcinogen as a fag. We will have to turn our attention to that as doctors, whatever we do as a result of the legislation. Have you tried to grapple with that and come up with any solution?

(*Professor Ashton*) I have not. Of course, school children start smoking at 12 or 14 years old, so that presents a difficulty. I suppose that people suffering from MS who smoke it would be ideal candidates. Apparently, 50 per cent of the young population have experience of this. So much depends on dosage because, like smoking, the effects are cumulative. I am not sure how easy it would be to get hard information.

(*Professor Nathanson*) I think that it is something of which doctors will become increasingly aware and will keep records of patients throughout their lives to try to get them to allow their doctors to record recreational and medicinal drug use. The difficulty is: Who has access to medical notes? This is a major issue. At the end of the day, patients do not tell doctors things if they believe that their notes will be accessed for other reasons and yet that is the only way that we will be able to disentangle the complexities of different drug use. There are many different recreational drugs in which increasingly there will be a need to have an idea of lifetime exposure—this is also true of a number of other drugs—to look at long-term effects. It is much better to have a large epidemiological study covering the majority of the population than to follow up a small group of patients, in exactly the same way that we obtained information on smoking cigarettes.

Chairman

61. In your report you talk about the hazards of smoking herbal cannabis, but you also say that smoking has advantages as a mode of administration, especially for dealing with vomiting. Can you think of any way of capturing the advantages without involving the hazards? We understand that manufacturers in the States produce cigarettes with a standard dose of cannabis.

(*Professor Ashton*) As to “standard dose of cannabis”, there are 60 different cannabinoids in cannabis. I presume they mean a standard dose of THC (tetrahydrocannabinoid) which for a start does not mean a standard dose of the other cannabinoids. There are methods of administration being developed, including inhalers, sprays, snuff-like substances and suppositories. Suppositories may not be very popular in England, although the French may like them. It is very well absorbed by that method. Skin patches are also being explored. I do



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Chairman *contd.*]

not believe that that is very likely because cannabinoids are so fat soluble that they spread on skin without being absorbed. The only way to overcome that problem is to develop inhalers.

(*Professor Nathanson*) A lot of work is being done on aerosols and inhalers of various kinds, partly related to removing CFCs from asthma inhalers. This is a very useful route of administration. I have no doubt that a lot of fat soluble drugs will be available in this form. It is now easy to use measured doses and it is a very acceptable method of administration. For cannabinoids, pure drugs could be administered in this way. One gets rid of the disadvantages. It is also portable and does not have the unwanted elements of rectal suppositories which at the moment are probably the most effective way of administering measured doses.

62. If one takes cannabinoids by mouth the absorption is very irregular, is it not?

(*Professor Nathanson*) Indeed. As with other soluble drugs, depending on the preparation it is not a measured dose.

*Lord Nathan*

63. Is it fair to talk about cannabis as if it were the same thing? In preparing for this enquiry I read about the use of cannabis in the previous century. Certain articles indicated that cannabis grown in India was very good at giving a "high", whereas what was produced in north west Europe was absolutely useless.

(*Professor Nathanson*) That is absolutely true. The fact is that different sub-species have very different doses or amounts of psycho-active constituents. Increasingly, the recreational drug available in the general market has been much stronger than that generally available in the United Kingdom only a few years ago, and that is a very important measurement. It is very difficult to compare the effects of smoked cannabis 10 or 20 years ago with those of today because the same weight of herb will not have the same weight of active substances.

*Chairman*

64. This was true of many drugs in the past. One example is digitalis. When the pure substance was manufactured those difficulties were removed. But that did not detract from the value of digitalis before digoxin was developed?

(*Professor Nathanson*) No. The same applies to tincture of cannabis. If it was always exactly the same herb used in making the preparation one would have some idea of the likely therapeutic effect. The difficulty is that when people use a variety of different sources there will be widely different amounts of active constituent, and that is not acceptable. At least for digitalis effectively it was one species.

*Lord Soulsby of Swaffham Prior*

65. The BMA report states that THC remains in the body for up to 30 days. As far as long-term use is concerned, is the persistence of the substance in

adipose tissue additive so that the 30 days might extend to several months? What are the implications for the supposed therapeutic effect of the metabolites, some of which are even more powerful than THC?

(*Professor Ashton*) If one gives a dose of cannabis, that is got rid of in 30 days. Of course, if one takes another dose before the 30 days are up it is added to the first one, so the effect is cumulative. As to whether it matters, it depends on what you are looking for. According to the literature, the physical effects of blood pressure, ocular pressure, lung dilatation, spasm and so forth are much shorter lived than the mental effects, which means that one must allow for a certain accumulation. Eventually—perhaps in months—that reaches a plateau. Therefore, the cost of dealing with the symptoms, unless one can separate the effects by research, may well be a degree of cognitive mental impairment. But as with any medicine, whether it be the opioids or others having a depressive effects on the central nervous system, one must balance the severity of the illness and the efficacy of the treatment for the particular condition being treated against the ill-effects of the drug. Yes, it does matter. That is one reason for trying to separate them. However, you probably cannot get rid of it given the nature of the drug.

66. In view of the concerns that you expressed about passive smoking, on the additive basis it seems that even the intake of small amounts of smoke will eventually reach levels that are considered unsatisfactory?

(*Professor Ashton*) That might be particularly so in the case of children. The levels of cannabinoids that one gets from passive smoking are very low. However, we do not know the exact effect. Children are more susceptible. There are cases where children have been in a coma because they have taken their parents' stuff. I was thinking more of the smoke constituents. If one has an individual cannabinoid that risk will disappear, unless the child takes the tablets.

67. Given the production of the metabolites in the adipose tissue, do the metabolites always break down at the same rate?

(*Professor Ashton*) Strangely enough, they fluctuate. In seeking to equate levels of metabolites in blood or urine, for example in driving impairment, the process is a difficult one. They go up and down and vary in different people; individuals metabolise it differently. There is not a smooth relationship between the metabolite and any effects.

*Chairman*

68. Does the accumulation of the substance take place mainly in the fatty tissues?

(*Professor Ashton*) Yes, but it recirculates. It is stored in the fat but there is always a little coming out. It then goes into the brain which is full of fatty tissue anyway.

69. The pharmacological dynamics are such that the amount released into the blood and plasma will not be sufficient to cause the other side-effects. But in



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Chairman *contd.*]

the brain, which has a lot of fat in it anyway, it may be more serious?

(*Professor Ashton*) That is certainly true. It is well known that the effects on heart rate and blood pressure pass off quite quickly.

70. The accumulation would not affect them very much?

(*Professor Ashton*) No, except that people develop tolerance to it. The other side of the coin is that the body adjusts to having small amounts of cannabis in it. Although cannabis raises blood pressure in the first instance, in chronic smokers the effect is less.

*Lord Butterfield*

71. Are the receptors in all adipose tissue, or are they mainly in the fatty tissue of the brain?

(*Professor Ashton*) There are two types of receptors. One is called CB1 receptors. They are found mostly in the brain but some are in the peripheral nervous tissue. CB2 receptors are not in the brain but are in peripheral tissues. This may be useful therapeutically, because if you can get drugs that act simply on CB2 receptors they may have some pain-relieving effect without affecting the brain.

*Lord Dixon-Smith*

72. Can we turn to the impact on human performance? Section 5 of Professor Ashton's paper deals with the effect of cannabis on complex tasks like driving. How long do those effects last? How do they compare with the effect of other licensed medicines? Would the answer be different if one was talking about occasional recreational use of cannabis, heavy recreational use or long-term therapeutic use? Would it be possible to set safe limits for cannabis in the blood stream—if there can be safe limits—as has been done with alcohol?

(*Professor Ashton*) How long does the effect last? It depends very much on the performance with which one is concerned. For a simple reaction time task the effect does not last long; for a divided attention, complicated task like driving, or flying an aeroplane, the effect can last for over 24 hours, even 48 hours, as a result of a small dose from a modern joint. But one may not notice it in everyday performance. Does it matter? There is a difference between occasional recreational use, as long as you do not drive afterwards, and chronic use. There is definitely a mental impairment problem. That will apply also to people who take cannabinoids medicinally that have that effect. It may well affect their day-to-day living and ability to climb up stepladders, for example, because it affects balance. Their short-term memory and ability to handle machinery at work and in the home, even kitchen knives, can be affected. That is true of people who use morphine for chronic pain. It is just something that must be taken into account if someone has an illness. A certain amount of compensation can take place. But for chronic recreational users there is a real risk in performance, such as driving. It would be very helpful to have a test as there is for alcohol. Unfortunately, at the moment it is not possible to do that. First, no research has been done to compare individual levels with

particular performances. Secondly, because of the cumulative effects and the slow excretion of the drug it is very difficult to tell when the person has taken his or her last dose of cannabis. It might have been a month ago. One has a clue. If one finds pure THC in the blood—the active substance—one knows that the individual has taken it fairly recently; if one finds the metabolites only one knows that it occurred a bit further back. But one still does not know how much the individual has taken and how much it will affect performance. It is not like alcohol which is a very simple drug with a known excretion rate that can be readily measured and tested against performance.

(*Professor Nathanson*) With all of the different constituents and breakdown products of cannabis, some of which are centrally active and some of which are not, it seems unlikely at the moment to be able to produce a test that relates a blood level of a mixture of substances, or one substance, to a particular level of psychomotor impairment. I suppose that it could be done with a lot of research. One would then need to decide whether that is also true for all the different types of cannabis. Do they all break down to the same kinds of levels of the different active constituents? The task would be a complex one. The question of the effect on driving performance worries most of us. It may mean that perhaps the best route to prosecution is driving without due care and attention rather than the simple test route which is possible with alcohol.

73. Can we turn to the problems of withdrawal from the use of cannabis? Professor Ashton's paper indicates that cannabis is at least potentially addictive, but the BMA report says that the withdrawal symptoms are mild and short-lived. How does the degree of addictiveness compare with other substances, both legal and illegal? In the suggested therapeutic contexts, is this a problem anyway?

(*Professor Ashton*) I think that the report says "are reported to be mild and short-lived", which represents a difference. First, most trials of the withdrawal effects of cannabis, of which there are very few, have been only short term. We know from long experience—it was not known at the time—that, although the withdrawal effects of benzodiazepine tranquillizers were supposed to be mild and short-lived, they can be very long and drawn-out. Secondly, there have been no trials of withdrawal effects in therapeutically used cannabis or cannabinoids—or at least no controlled trials—although it is known that there are rebound effects, for example with glaucoma. Although at the time it is given it lowers ocular pressure, when it is stopped it bounces up higher than before. The trials that have been made have taken place on volunteers who were cannabis smokers but in controlled conditions. They showed quite severe and definite withdrawal effects when whole cannabis was withdrawn without their knowledge. The drug was taken by mouth. The withdrawal effects were very similar to those from alcohol, sleeping pills and tranquillizers: tremor, restlessness and insomnia. Cannabis has many of the effects of alcohol, tranquillizers and opioids, but we do not know what would happen if they were used therapeutically. Individual cannabinoids have not been tried. We believe that there may be withdrawal



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued

Lord Dixon-Smith *contd.*]

effects if someone is using it chronically. That can be important therapeutically. As with many drugs, if you want to withdraw it you have to do it slowly. As to how they compare with other drugs of addiction, we know now, admittedly from animal experiments, that cannabis affects the same part of the brain as cocaine, opium, amphetamines, alcohol, nicotine and all addictive drugs. It liberates the same transmitter and acts in the same way. That is probably how one gets a "high". All drugs that have that action have been shown to be addictive in man. That is why I say that potentially it is an addictive drug. There is clinical evidence that of the preparations now available there is an increasing demand by patients, who often will not give their names, for help with withdrawal from cannabis. I have seen this in students at Newcastle. They do not go to the health service for help because they do not want to give their names; they go to the student counsellors. I have talked to them and had contact with others in Newcastle. They get quite severe withdrawal problems. Even students who want to get on with their studies because they know that cannabis is affecting their memory cannot get off it after they have used it for a certain length of time.

*Lord Porter of Luddenham*

74. Professor Ashton, am I right to conclude from what you said earlier that you believe that it is probably pharmacologically impossible to get the therapeutic effects without the psychoactive effects and that the "high" may be part of the therapy?

(Professor Ashton) I did not say that it was impossible. Up to now the studies made on pain relief show that in the CB1 receptors, the central ones, it is difficult to separate the psychoactive effect and pain-relief effect. But cannabinoids also have anti-inflammatory properties which would affect the CB2 receptors in the periphery. One might be able to separate the effects in that way. Even for vomiting there are cannabinoid preparations, like delta 8 THC as opposed to delta 9 THC, that appear to have less psychoactive effect. In one study Professor Mechoulam looked at 500 children and gave up the trial because delta 8 THC stopped the vomiting and did not have the psychological effect of delta 9 THC. He switched all of them to delta 8. It seems that in some conditions it is possible to do that, but we do not know about the total. Certainly, people with multiple sclerosis, including Clare Hodges who is mentioned in the paper, take doses which give psychological effects. In her deposition she said that she took one third of an ounce which is about 8 to 10 mg of THC<sup>1</sup>. We know that 2.5 mg of THC can produce psychological effects. It may be difficult for some conditions or it may be a good thing in multiple sclerosis in that it has a calming effect and also relieves symptoms.

75. There will always be a danger, will there not, that cannabis supplied for medical use can be diverted to recreational purposes?

(Professor Ashton) Unfortunately, that has happened with benzodiazepines, amphetamines and ecstasy, for example. It is very difficult, but I believe that pure cannabinoids would be much easier to control than cannabis itself.

76. Are recreational users likely to be interested in it in any form other than smoking it?

(Professor Ashton) I am afraid that some might.

(Professor Nathanson) We must recognise that if a pure cannabinoid has a strong psychoactive effect—because that is the effect that is looked for—it will become an attractive substance for recreational use. But that is the effect which in large part is not the desired effect because we are not considering producing cannabinoids to be primarily psychoactive substances; we are looking for other effects. If we find cannabinoids that have minimal psychoactive effects but are powerful reducers of muscle spasm or other effects they will be pretty unattractive to recreational users because they will not have the effect that they are looking for.

77. Do the cannabinoids taken by mouth or other than by smoking give one a "high"?

(Professor Ashton) Yes—and also dysphoria. A lot of people have adverse psychiatric effects, like acute anxiety, depression, hallucinations and all sorts of things. Some also get a high.

*Lord Butterfield*

78. Is it possible to separate out the cannabinoids by fixing on certain receptors which may tell one that this will be good for pain or for other things? Would that be a sensible research programme?

(Professor Ashton) I think that it is very well worth pursuing. At the moment it has not got that far. But there are antagonists. One could test drugs that might act on those receptors and use an antagonist for one of them to see if it worked.

*Lord Soulsby of Swaffham Prior*

79. To pursue the adverse effects of the use of cannabis, a fair number of comments have been made, some of which appear to me to be somewhat anecdotal, about the effect on the immune system. How far has that been probed in terms of the basic mechanisms for the effect on the immune system? Is it a temporary or permanent effect?

(Professor Nathanson) There is a need for a lot of further research on this matter. There are animal studies to suggest that there is some interference with different aspects, but it is not clear what the relevance of this would be in man, particularly in chronic use. One of the most important issues is the concern that arises if cannabis, as opposed to cannabinoids, were to be used in immune-suppressed patients. There would be a particular concern about the presence of fungi and microbes in the plant, which are pretty widespread, and the danger of inhaling them and causing infections. I am thinking of the more immuno-compromised patients. For example, those on cancer chemotherapy would be at particular risk. But there is also a need to look at cannabinoids and whether they have an effect on the immune system.

<sup>1</sup> Note by the Clerk: Miss Hodges uses this much cannabis *per week*, not all at once (p 28).



21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

That can be done only by looking at the individual drugs in clinical trials.

(*Professor Ashton*) Very little is known about this. Some of the anti-immune effects may be due to smoke constituents and not cannabinoids. The cannabinoids may have an additional effect, but it is known that cigarette smoke has an anti-immune effect. Not enough is known about it, but it is complicated.

80. With respect to the effects of opportunistic organisms or other bodies, the position is slightly different. In cannabis users is there a greater incidence of influenza, viral infections and more common colds to give an impression of the suppression of one form of mediated immunity versus antibody-mediated immunity?

(*Professor Ashton*) This has been looked at in Australia and the States. One study found that the incidence of progression of HIV infection to AIDS was not increased in cannabis smokers, but there is some evidence that the incidence of common colds, chest infections and so on is increased in chronic cannabis users. However, that may be due to the smoke. We do not know whether it is due to the cannabinoids.

Chairman

81. But many of the CB2 receptors are on cells of the immune system, are they not?

(*Professor Ashton*) Yes, in the spleen and other blood cells. CB1 receptors do not seem to mediate that response.

Lord Kirkwood

82. What has been the reaction to the BMA report from the Government, the Royal Colleges, patient groups and so forth? What action would you like to be taken consequent upon your report, and by whom would you like it to be carried out?

(*Professor Nathanson*) The reactions so far have been extremely positive and very encouraging. I think that it has been well received because of the distinction that we have made between cannabis and cannabinoids. Everyone wishes to find better therapeutic options for those patients who so far have not been offered all the help that could be made available. There are distinct advantages in going down the cannabinoid route because of the need to get rid of many of the unwanted effects. One of the matters we have suggested is the need for co-ordination to draw up guidelines for good research practice. To design good research in this area is a complicated matter. We are delighted that the Royal Pharmaceutical Society is putting together and expanding a group that is doing clinical work on cannabinoids. We understand that that is to be chaired by Sir William Asscher, a past chairman of the Committee on the Safety of Medicines and a great expert on research trials. A number of other very good people are involved in that. There will be an ability, both to produce better research and help focus the people doing research, to talk to others so that there is a good exchange of views; so that as cannabinoids are developed, both the natural extract

and synthetics, there is the least possible time delay between development and proper clinical trials and the sharing of information. We have not at present had a response from the World Health Organisation. At the moment I think it is unlikely that WHO will consider changing its classification of cannabinoids. That is not a major problem because there is an alternative route for the Home Office in freeing up the licensing of new cannabinoids for more therapeutic indications. We have had a very positive feedback from the Department of Health and Home Office on the need to ensure that there are no unacceptable delays to licensing properly constituted research on cannabinoids, which is an extremely important part of the process of producing new therapeutic instruments for different patient groups.

Lord Nathan

83. We are told that the take-up of nabilone and dronabinol as anti-emetics is low and that the drug companies are not interested in cannabis-based medicines. Is that so? If so, why given the head of steam behind the medical use of cannabis?

(*Professor Nathanson*) There are several reasons for the relatively low take-up, one of which is that there are other very powerful and new anti-emetic agents available on the market, some of which have been found to be very helpful in exactly the same patient groups for which nabilone and dronabinol are considered. Where one has an effective alternative and there is good research for the use of that substance and no difficult legal issues, particularly in terms of having to import dronabinol on a particular named patient basis, clearly it is easier for doctors to use the established regimen. Separately, to a degree I argue with the "head of steam for medical use" concept. I believe that doctors are, quite rightly, being fairly cautious because they are aware that cannabis is not a simple drug but a complex agent with many different active constituents. One of the purposes of our report was to give to doctors information about cannabis and cannabinoids which would help them to decide whether or not agents such as nabilone and dronabinol would be of help to their existing patients. It would not surprise me if the uptake in anti-emetics increased because of the reading of the report. I am absolutely certain that if there is good research and new drugs come forward which are widely reported in the medical literature, they will also be used with the proper and appropriate indications. Clearly, the more research there is and the more that is reported and seen to provide a proper basis for prescribing, the more drugs will come into relatively common use as appropriate and as indicated by that research.

Chairman

84. There is still very little activity going on in the pharmaceutical industry other than activity on the two receptors.

(*Professor Ashton*) Of course, use in the treatment of vomiting due to chemotherapy for cancer is a very small market anyway. To widen the scope for doctors



21 April 1998]

PROFESSOR VIVienne NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Chairman *contd.*]

to prescribe drugs for common chronic conditions will increase the interest of drug companies enormously. It was not worth their while to do research into drugs that doctors could not prescribe anyway, but now one can prescribe dronabinol and nabilone for multiple sclerosis. If this is widened and research is going on into common diseases I believe that drug companies will become very interested.

*Lord Butterfield*

85. In the case of multiple sclerosis and other neurological disorders involving spasticity, your excellent BMA report calls for further research as "a matter of some urgency", to quote page 37. Can you see ways round the difficulties, practical, legal and ethical, of conducting proper clinical trials? For example, would a cross-over trial or a trial with a psychoactive placebo be practical? Randomised double-blind trials have been done in the context of vomiting due to anti-cancer drugs. How were those trials managed? I and other members of the committee would be most interested in any reflections that you have on the question of organising satisfactory clinical trials.

(*Professor Nathanson*) This is another area in which we have been delighted by the Royal Pharmaceutical Society's expansion of its clinical cannabinoid group. The first remit that it has agreed to undertake is to try to set guidelines for clinical trials and address the extremely difficult issues of designing trials to make them both ethical and practical, whether they be double-blind, cross-over, placebo-controlled and so on.

(*Professor Ashton*) We have discussed this with the Chief Medical Officer. It is very difficult to design trials. The clinical cannabinoid group's experts are meeting for just that reason. For example, multiple sclerosis is such a heterogeneous condition, with all kinds of symptoms, that one must go for individual symptoms like spasticity, bladder control or whatever which can be measured objectively. One uses a cannabinoid in a known dosage. One will have to do preliminary trials to establish optimal dosage and frequency which may have to be individualised. One may want to look at the effects of a combination of two cannabinoids, such as cannabidiol and perhaps nabilone. The trials would also have to be of long duration, first because of tolerance resulting from long-term use and, secondly, because multiple sclerosis is a condition with remissions. One then comes to the difficult question of cross-overs and placebos. I would rather leave that to the clinical cannabinoid group. It would be possible to do cross-over trials with something like diazepam or baclofen, a muscle relaxant which is already in use, depending on what symptoms one is looking for. The task was easier in the anti-emetic trials because there were standard drugs in use—for example prochlorperazine, which is psychoactive—by which one could randomise patients. One would have to think in terms of double-blind and cross-over trials. But I am not an expert and there are others in this field who can look at that.

86. Do you see any possibility that the various medical charities, or perhaps the Medical Research

Council, can become involved? If there were to be a trial, it would be terribly important for it to be acceptable across the board, so that when it was finished no one could say that had not been done and therefore the whole process was a waste of money. What is your view of the medical charities research panels of the MRC? Are they becoming concerned?

(*Professor Nathanson*) Our feeling is that the Medical Research Council and particularly the charities concerned with particular medical conditions—the MS Society and other such groups—may well become interested, particularly if there are guidelines on good research design and they can be certain that any trial is well designed and will give accurate answers. Some of the reluctance to fund trials has come from concern about the quality of research. Clearly, if research quality can be guaranteed people will be happier to fund it.

*Lord Kirkwood*

87. I believe that you have seen the written evidence from the Association for Cannabis Therapeutics. Please give us your comments on that association's evidence. In particular, criticism has been made of the BMA report's focus on single cannabinoids since there may be synergistic effects from herbal cannabis. Do you feel that that has any substance?

(*Professor Nathanson*) Yes and no. Clearly, we looked at the research evidence on both cannabis and individual cannabinoids and favoured the approach of looking at the latter. We accept that it is entirely possible that in future the best agents for treatment may well not be single drugs but an amalgamation of two or three agents. There may be synergistic effects. The difficulty is that with cannabis one is looking at 400 active agents. I do not believe that that is the best modality of any treatment. There are many medical treatments which have more than one agent with different effects which are more than just additive. Antibiotics is an example and there are many others. It may well be that the cannabinoids which are useful for different treatments include a different mixture, natural or synthetic, of pure drugs in measured doses. Another interesting issue is that the synergies may come about with a very different balance of agents from those which exist in the current mix in cannabis. Another problem is that it is not known how many of the agents in cannabis detract from any potential therapeutic benefit. That is also possible, just as the effects may be purely synergistic or additive.

(*Professor Ashton*) It is known that some are antagonistic.

88. If there are 60 different cannabinoids it means that there will be a very long research programme?

(*Professor Ashton*) Not all 60 are available. They have been categorised, but probably four of the natural ones and some synthetic ones will be the maximum.

(*Professor Nathanson*) With current computer modelling and other techniques in practice most pharmaceutical companies will want to try all 60 if they are readily available and extractable. It is much

21 April 1998]

PROFESSOR VIVIENNE NATHANSON  
AND PROFESSOR HEATHER ASHTON

[Continued]

Lord Kirkwood *contd.*]

more likely that there will be designed versions available by the use of that technology.

*Chairman*

89. Another reason why it is difficult to get more clinical studies done is that herbal cannabis is readily available illegally. That may well be one reason why it is more difficult to organise trials for the pure cannabinoids?

(*Professor Nathanson*) We have no idea what the effect of that would be. Another important issue is the availability of herbal cannabis within the very patient groups. One must ensure that those patients are not put into a trial the day after they stop taking herbal cannabis. One would have the problem of the withdrawal effects. It may well be that a potentially very good beneficial effect of a cannabinoid is not seen because of the withdrawal effect from the complex agent. Those will be challenges for the group that tries to draw up good protocols for clinical trials.

90. You referred to 400 active ingredients. Surely, not all 400 ingredients are active.

(*Professor Nathanson*) There are 400 ingredients, but not all of them are cannabinoids. There are 60 cannabinoids, and not all of them may be active. Certainly, there are 400 ingredients which are chemically active.

91. It was the word "active" which concerned me.

(*Professor Nathanson*) They are not active in the "cannabinoid" sense.

*Lord Soulsby of Swaffham Prior*

92. The BMA reported that there should be a relaxation of the regime of Home Office licences. As I understand it, in order to do research into the cannabinoids you need a Misuse of Drugs Act licence from the Home Office. How difficult is it to get a project licence from the Home Office to undertake work with cannabinoids?

(*Professor Nathanson*) At the moment, we are hearing of a considerable delay. We do not know how long that is, but we hear of perhaps 14 applications that have not yet received a response. We do not know the details of all those research applications and there may be good reasons for those delays, but there is concern that while there is an interest in this matter the licensing process may hold up good research inappropriately. We believe that part of the remit of the group looking at research protocols is to try to help the Home Office to set such guidelines for research against a licence application and to make it easier for the department to detect which are the good protocols that can be quickly given the appropriate licences.

93. The Animal Procedures Committee periodically holds small seminars to look at the research needs in this area. Has the suggestion been made to the Home Office inspectorate that perhaps there could be a closed workshop to look at research into cannabinoids?

(*Professor Nathanson*) I do not believe that it has, but it sounds an excellent idea.

94. [Unallocated]



---

TUESDAY 28 APRIL 1998

---

## Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.  
Perry of Walton, L.  
(Chairman)

Porter of Luddenham, L.  
Soulsby of Swaffham Prior, L.  
Walton of Detchant, L.  
Winston, L.

---

**Memorandum by the Alliance for Cannabis Therapeutics****PERSONAL TESTIMONY FROM CLARE HODGES**

1. I am a 40 year old married woman with two children and I first developed multiple sclerosis when I was 25 years old. I started by experiencing spasticity, nausea and loss of sensation. Over the years I have developed further problems of more sickness and stiffness, poor appetite, and great discomfort in my bladder. This discomfort resulted in me going to the toilet at least 12 times a night and not sleeping. This in turn exacerbated other symptoms of impaired vision, poor balance, fatigue and susceptibility to infection.

2. I had been prescribed many different medicines for the various problems. None of these medicines provided sustained relief. Baclofen, Valium and ACTH all had unacceptable side effects in my case. Temazepam did help me sleep but made me anxious and I found it very habit-forming. In particular I sought relief for the bladder problem. I was not helped by Imipramine, Desmopressin or Oxybutynin, and took a daily dose of Nitrofurantoin to prevent constant urinary tract infections.

3. I had been treated for nine years with orthodox medication, but as I had not been able to find relief for my bladder, I decided to try to treat myself. I read an article in an American Journal about how some doctors report that people with multiple sclerosis benefit from using cannabis. Before I did anything, I asked all the doctors I see about the advisability of trying cannabis. They were interested but didn't know much about cannabis. They all said it couldn't do me much harm in moderate quantities, and it was probably safer than many of the medicines they could prescribe.

4. My only experience of cannabis was occasional, embarrassed experimenting in student days, and I did not know how to obtain any. A friend got hold of some cannabis for me and showed me how to smoke it with tobacco. It was effective within about five minutes. The tension in my bladder and spine melted away, and I felt less sick and stiff. I could move and generally function with greater ease and I slept soundly that night without medication.

5. After a few months of taking cannabis, I found I was able to reduce the doses of my prescribed medication, so that I did not take anything for my bladder or to help me sleep. I no longer take daily antibiotics as I do not have such problems emptying my bladder. Cannabis has not "cured" my MS, but my general health is very much improved. As well as relieving specific acute problems such as bladder dysfunction, discomfort in my spine and nausea, it has helped long-term problems such as poor sleeping and lack of appetite. My MS symptoms vary considerably. Sometimes I appear quite able-bodied for short periods, and at other times I look and sound very handicapped. Similarly I can be cheerful about my situation, but when the MS is bad, I become very introspective and negative. I know a lot of the therapeutic benefit is psychological as well as physical. MS makes me slightly under par all the time, so that even the simplest task takes an enormous effort and leaves me exhausted. I don't have to get "high" for cannabis to lift my mood, make me feel calm and positive and able to carry on more normally. This kind of mood-altering effect often seems to be desirable in serious, chronic illnesses judging by the large numbers of people with multiple sclerosis who are prescribed anti-depressants and tranquilisers.

6. The relief cannabis gave me has been sustained over the years, the main improvement being bladder control. It has not helped all the symptoms I have. For example it has not affected my impaired vision. I do not feel addicted to cannabis any more than any ill person is "addicted" to their medication. If, for some reason (eg cost or availability) I cannot take cannabis, I do not "crave" it in any way nor experience withdrawal. All that happens is that my MS symptoms return.

7. I have now been using cannabis for six years. For the first two years I grew it at home, dried the leaves and took them in hot drinks. I stopped growing it because I was afraid of being prosecuted. I now buy cannabis via friends and either take it orally, or more usually smoke it with herbal tobacco as otherwise it is very hard to regulate the dose. With the cannabis I had grown it was relatively easy to work out how much to take orally.

*28 April 1998]**[Continued]*

8. At my request, I was prescribed Nabilone (the currently available cannabinoid) by my Neurologist. I hoped that it might be as helpful as cannabis and it would spare me the trouble, cost and illegality of funding supplies myself. I took a dose of 1 mg Nabilone daily for three nights, but I found it made me feel rather confused and clumsy. As Nabilone was causing problems and did not seem to reproduce the beneficial effects of cannabis, I stopped taking it.

9. It took me several months when I first started taking cannabis to work out how much I needed. This amount varies slightly depending on whether the MS is stable or not, but in general it has not increased over the years, and remains at a constant of about  $\frac{1}{3}$  ounce of herbal cannabis per week, either smoked or taken orally.

#### FOUNDING AND ACTIVITIES OF THE ALLIANCE FOR CANNABIS THERAPEUTICS

10. The Neurologist I see was very interested in my apparent improvement, and in 1992 put me in touch with two other of his patients with MS who had similar experiences with cannabis. After we three patients discovered how much scientific evidence there was to support our experiences, we decided to form a group to campaign for more research into the therapeutic use of cannabis. We thought hard before we did this, because so many treatments and "cures" are claimed for multiple sclerosis which give false hope. We were helped to set up this campaign by the Washington-based patients' organisation the Alliance for Cannabis Therapeutics, from whom we took our name. The other two patients were not able to continue their involvement in the campaign because of family reasons, so it fell to me to organise it on my own.

11. "Clare Hodges" is a name I adopted for the campaign. This is because to begin with I was very much a lone voice and was worried about being identified. This was especially because my children were very young and had yet to embark upon school life. My birth name is Elizabeth Clare Brice, which I would be happy to use now that the issue is more accepted, but I fear it would only confuse matters. "Hodges" was my (now deceased) mother's maiden name, and she was pleased and proud that I used it for the campaign.

12. Over the years the ACT has been contacted by over 2,000 people, many of whom have given the campaign practical and moral support. The ACT is now a loose affiliation of patients, doctors and politicians who have agreed on aims and objectives. We are campaigning for research into medical preparations of natural cannabis and for these to be made available on a doctor's prescription while research is going ahead. We are asking for research into natural cannabis on the grounds that we know now that cannabis can be effective and is safe enough to be prescribed by a doctor. If a cannabinoid, or combination of cannabinoids is developed which is as effective and safe as natural cannabis, we would readily accept it. But, at present, no such medicine exists, and there are people who need treatment now.

13. We are not campaigning for the general legalisation of cannabis. Indeed even if cannabis were legalised, we would still be campaigning, as we think seriously ill people should get their medication from their doctor, and not have to provide it for themselves. Similarly, the objectives of the ACT would not necessitate cannabis being legalised. Preparations of cannabis could be available for medical use while still being illegal, as is, for instance, diamorphine/heroin.

14. We have not applied for charitable status and do not have any external source of income. We are funded entirely by donations from patients and doctors.

15. The BMA approached the ACT when it was writing its report, "Therapeutic Uses of Cannabis" in 1997. The ACT helped them by providing information and contacts. (We are acknowledged and thanked in the report.) We have corresponded with, and helped doctors wishing to research into cannabis and cannabinoids, especially Dr William Notcutt, Dr Roger Pertwee and Dr Geoffrey Guy.

16. The ACT has taken two delegations of supportive doctors and politicians to the Department of Health, one in 1994 and one in 1997. In both we asked for medical preparations of natural cannabis be made available for research, and for prescription on a named patient basis while research is going ahead. We stressed that we wanted natural cannabis as well as isolated cannabinoids to be researched.

The delegation in December 1997 consisted of:

Professor Patrick Wall, Professor Emeritus in Physiology, St Thomas' Hospital;

Dr William Notcutt, Consultant Anaesthetist, James Paget Hospital;

Dr Geoffrey Guy, Chairman, Phytopharm pharmaceutical company;

Dr Giles Elrlington, Consultant Neurologist, Colchester General Hospital;

Clare Hodges, Director, Alliance for Cannabis Therapeutics;

Austin Mitchell MP;

Gordon Prentice MP;

Baroness Cumberlege and Lord Whaddon both intended to come on the delegation, but were unable to attend.



28 April 1998]

[Continued

17. We have received widespread support from doctors, especially GP's but also hospital consultants. This support was reflected in the vote at the BMA annual conference in July 1997, where a large majority voted for the motion that was put before them that "certain additional cannabinoids should be legalised for wider medical use". The motion is not very clear or specific, but the vote shows a confidence from doctors in the therapeutic potential of cannabis. Over fifty patients have told the ACT that their doctors have recommended that they try cannabis for symptomatic relief.

#### INFORMATION GATHERED FROM CORRESPONDENCE TO ACT

18. The ACT has received over 2,000 letters and faxes, mainly from patients, doctors and health workers. Of these, around 200 patients with multiple sclerosis have written in some detail about their experiences of using cannabis. People with other conditions, for example spinal injury and cancer have also written about their use. In this submission I am referring only to the patients who use cannabis for multiple sclerosis as this is the area where we have most information. (Breakdown of correspondence on page 10.)

#### *Dr Pertwee research based on correspondence to ACT*

19. In 1994 Dr Pertwee of Aberdeen University wanted to conduct research into the "perceived effects of smoked cannabis on patients with multiple sclerosis". The ACT was in the unique position of being able to help him by sending out a questionnaire which he had constructed. We sent it to people with multiple sclerosis who had written to the ACT about their use of cannabis (at that time around 120). The ACT in America did the same for Dr Pertwee's co-authors in American universities. The authors of the paper analysed and catalogued the information from these questionnaires and published the results in "European Neurology". This analysis takes full account of the possibility of a strong placebo effect, and concludes that for pain and spasticity in particular, there are strong indications of significant improvement. Dr Pertwee summarises the findings:

"Among the 112 MS patients who use cannabis—illegally under current laws—almost all reported multiple benefits. Improvements included reduction in muscle spasms when falling asleep (96.5 per cent), decreased spasms when waking at night (93.2 per cent), relief from pain in the legs at night (92.3 per cent), from arm or head tremors (90.7 per cent) and from depression (90.6 per cent)."

#### *General observations from experience of running ACT*

20. Dr Pertwee and his colleagues were able to analyse single answers to specific questions. The following are more general observations based on the correspondence the ACT has received, and also on many conversations either by phone or in person with patients about the use of cannabis. I have been talking to people with MS and to doctors about the subject for six years, and have built up a broad overview.

21. It is impossible to know how many people with MS use cannabis at present, and of these how many derive benefit. In an MS Society "Information Day" in 1996, Peter Cardy, the Chief Executive, asked the MS patients assembled in the hall to raise their hands if they had taken cannabis for symptomatic relief, and then to raise their hands if they had found no benefit. The majority in the hall had tried cannabis, but only a handful said they received no benefit. It is unlikely that this is representative of MS patients in general, but it is worth noting.

22. My impression is that most people with MS do not use cannabis, but would very much like the opportunity to find out, legally, if it could help them. Many people with MS find they do not get any sustained relief from their condition from conventional medications. A lot of patients, especially those with pain, are very distressed and disillusioned because they have not been helped. It is widely recognised that for many patients with multiple sclerosis there is at present no acceptable medication, and sufferers look for palliative care.

23. As with any medicine, some have tried cannabis and find it gives them no relief, or even makes their symptoms worse in the short term. Two people have told me that it can make their balance and co-ordination worse for half-an-hour or so and the ACT has received five letters reporting no benefit or unwanted effects from cannabis. I would have expected to come across more negative accounts, given that the people who write to us are often very naive about cannabis and are treating themselves without guidance. Again, it is difficult to know how representative these figures are.

24. The people who do use cannabis and derive benefit have varying degrees of disability, ranging from the relatively mild to the very severe. In the early days of the ACT I was very struck by how similar were people's accounts of the benefits they had experienced. This was before they could have read the accounts given by others in the newspaper articles which were later written about medicinal cannabis. The most common reported benefits are pain management, reduction of muscle spasms and relief of the depression associated with chronic illness.

25. However, one of the greatest benefits people report is that they feel they have some control over their

28 April 1998]

[Continued

disease, often for the first time. It is not only that cannabis relieves specific symptoms more effectively than other medication. People are also greatly helped by treating themselves. We know how beneficial it is for people to self-medicate for pain control, and it seems that the same is true for MS. As well as giving patients a feeling of having some control, self-medication also seems a more efficient way to find the correct dosage. MS produces a variety of symptoms which get better or worse often very quickly and usually there is no clear pattern. With a disease so unpredictable, self-medication seems more helpful than treatment with regular doses of a fixed strength.

26. This benefit people gain from treating themselves probably explains why most people choose to smoke cannabis rather than take it any other way. The advantages in taking cannabis via the lungs is that the effects are much quicker and therefore easier to regulate. It is also preferable to use this way if the patient needs fast relief, from, for example, painful muscle spasms. Others want to avoid smoking and have developed ways of taking it orally, sometimes writing to the ACT with "recipes".

27. Nabilone does not seem to be an effective substitute for cannabis used therapeutically. I have talked to two people and had letters from twelve people who have been prescribed Nabilone. This is the synthetic cannabinoid currently available, and is not licensed for use in multiple sclerosis. However, some doctors do prescribe it for patients who want to try cannabis and do not want to break the law. Two patients said they found Nabilone helpful, but did not carry on taking it. Two found its side effects unacceptable, and all those who have taken both Nabilone and natural cannabis say that cannabis is more effective and easier to control. I have talked to two doctors—Dr Notcutt and Dr Elrington, who prescribe Nabilone, and they report similar findings.

28. Breakdown of correspondence sent to ACT:

#### 2010 Letters/faxes received

- 270 Patients who use cannabis therapeutically and find benefit
  - 200 Multiple Sclerosis
    - 50 Spinal Injury
    - 20 Other (epilepsy, depression, arthritis, AIDS, cancer)
  - 5 Patients who have tried cannabis and do not gain benefit or unwanted effects
- 50 Doctors
- 75 Health workers/organisations
- 1,500 Patients writing for information about therapeutic use of cannabis
- 120 Others (students, offers of help etc)

#### Additional breakdown

- 12 Patients prescribed Nabilone
  - 2 Beneficial effects
  - 2 No benefit or unpleasant side effects
  - 8 Preferred using cannabis

#### In defence of anecdotal evidence

29. The evidence submitted here is based on the experiences reported by people with multiple sclerosis who use cannabis for symptomatic relief. These testimonies given by patients are often dismissed as "anecdotal evidence". I would like to make three points about this.

- (a) Anecdotal evidence is often readily accepted about the negative effects of cannabis, but treated sceptically if it is about positive effects. For example, it is widely written that cannabis use can trigger underlying schizophrenia, but there is very little evidence for this beyond anecdotal.
- (b) The anecdotal evidence the ACT has received is consistent and well-established over six years. In a subject as under-researched as cannabis therapeutics, this must be taken seriously.
- (c) In many cases anecdotal evidence from patients has been a spur to medical advances eg the use of Imipramine for childhood enuresis when it was originally licensed for a different reason. The current interest in the therapeutic uses of cannabis has come about not through research by pharmaceutical companies and others, but as a result of patients giving anecdotal evidence.

Clare Hodges

Director, Alliance for Cannabis Therapeutics

31 March 1998



28 April 1998]

[Continued

**Memorandum by Professor Patrick Wall, FRS, DM, FRCP****ADDENDUM TO THE SUBMISSION BY THE ALLIANCE FOR CANNABIS THERAPEUTICS**

I very much support the BMA report and recommendations as I have indicated on that report: I have only one reservation. Here I wish mainly to update their report.

**BASIC SCIENCE:**

There is intense activity in universities and pharmaceutical companies on the subject. The annual meeting of the American Neuroscience Society in 1997 had 32 reports on cannabis and cannabinoids. The journal "Pain" will have six papers during the year on the effects of cannabis and related compounds.

- (a) Sources: Cannabis (with assayed potency) is now available from Hortopharm in Holland and is being developed in Britain. In addition large numbers of cannabinoids are being synthesised and investigated particularly by US companies.
- (b) Receptors: Two receptors have been analysed in full detail. One, CB1, is surprisingly widely distributed in the central nervous system. The other, CB2, is a component of a number of cells in peripheral tissue. However, the central versus peripheral separation of these receptors may not be precise since mRNA analysis shows an even wider spread of receptors than previously suspected.
- (c) Endogenous ligands: Two naturally occurring cannabinoids have been discovered in mammals. The situation now mimics the study of narcotic action as it stood about 15 years ago.
- (d) Antagonists: To both types of receptor are now available. The existence of these compounds will greatly facilitate pharmacological studies and the safety of human trials.

**ROUTES OF ADMINISTRATION**

- (a) Smoke: has the single advantage of rapid absorption but has the obvious disadvantages plus difficulty of providing a placebo and the lack of familiarity of many patients with smoking.
- (b) Suppositories: are available.
- (c) Nebulisers: are under development.
- (d) Patches: are under investigation.
- (e) Oral: has the advantage of simplicity but absorption is slow and variable. However, serum levels can be monitored.

**CLINICAL TRIALS**

- (a) Symptomatic Relief: It is crucial to take advantage of patients' reports that they have experienced only rapid onset short lasting relief of specific symptoms. None have claimed cures. This greatly simplifies the nature of trials that should be directed at single symptoms such as bladder control and not at overall diseases such as multiple sclerosis.
- (b) Target of Action: A number of the claimed beneficial actions such as on glaucoma, nausea, bladder control etc could be due to action on peripheral tissue rather than on the central nervous system. Basic studies suggest an anti-inflammatory effect of some cannabinoids. This suggests that trials of local application should be considered as well as systematic administration.
- (c) Dosage: Many patients report relief of symptoms at a dose short of those producing psychedelic effects. This is reminiscent of the treatment of cancer pain and post-operative pain with narcotics by PCA (patient controlled analgesia) where the patient titrates their pain down to a bearable level while still thinking clearly.

**WHY ARE THERE SO FEW RIGOROUS CLINICAL TRIALS?**

I know of only four UK Trials in an advanced planning stage. They are by Dr Pertwee in Aberdeen, Dr Fowler in London, Dr Ernst in Exeter and an open trial by Dr Notcutt in Great Yarmouth. I know of none in the States. It is a paradox that a topic of such intense scientific interest should receive so little clinical attention. One reason for this is outlined in the BMA report as the daunting and excessive bureaucratic control which artificially separates studies of cannabis from drugs such as narcotics. The other reason is the general social atmosphere which labels cannabis with every possible negative attitude. Again the situation mimics the attitude to the chronic use of narcotics some 25 years ago before strong characters such as Dame Cicely Saunders carried out rigorous trials. When there are so many avenues to explore in high profile subjects it takes a strong dedicated investigator to drive through an adequate trial of such a generally doubted subject in such a negative atmosphere. The House of Lords committee can make a very positive contribution by insisting that trials are necessary and should be facilitated.

28 April 1998]

[Continued]

## ONE RESERVATION ABOUT THE BMA REPORT

This otherwise excellent report focuses only on single molecules. This may be premature. Herbal cannabis contains a mixture of active compounds. It is too early to be certain if the therapeutic action is limited to one compound. Certainly sensible patients who appear to benefit from cannabis, do not report an equal benefit when given one of the single molecule cannabinoids. Cannabis may contain a synergistic mixture of active compounds. This is particularly likely now that we know there are at least two receptor specified loci of action. Therefore, while, of course, the therapeutic effects of cannabinoids must be explored, the action of herbal cannabis itself still needs definition.

27 March 1998

## Examination of Witnesses

MISS CLARE HODGES, Director, Alliance for Cannabis Therapeutics, and PROFESSOR PATRICK WALL, FRS, St Thomas' Hospital, were called in and examined; MR AUSTIN MITCHELL, a Member of the House of Commons, was examined.

*Chairman*

95. Tell us something, if you would, about the Alliance.

(*Miss Hodges*) My Lord Chairman, I am Clare Hodges, I am the Director of the Alliance for Cannabis Therapeutics. When the Alliance started in 1992 it was just myself and a few other patients with multiple sclerosis who had used cannabis and found it helped us greatly. We checked out the science that we could and we decided to campaign to get it taken seriously as a medicine. This was very new territory to us, dealing with drugs companies, doctors, researchers, politicians and we would not have got very far at all without the help of Professor Patrick Wall and Austin Mitchell MP who have both given enormous help and support to us. Professor Wall has examined the issue with great compassion as well as great expertise and he has brought it to people's attention. We knew very little about the workings of political machinery and we owe an enormous amount to Austin Mitchell who has adopted the cause in Parliament and has promoted the idea with great energy. I can only admire the way you have approached it. This is who we are.

96. What sort of numbers of membership have you got in the Alliance?

(*Miss Hodges*) We do not have a formal membership. It has mushroomed. It was not designed to be like this. Over 2,000 people have written in and I have talked to many people through contacts. 2,000 people have expressed an interest in being involved, helping or knowing more about it and these are patients on the whole. Doctors have got involved. We are talking about maybe 100 doctors who have got very interested usually as a result of their patients talking to them. There is a groundswell of support all over the place. Multiple sclerosis groups all round the place have lots of members who use cannabis to good effect and they are very interested in promoting the idea and they help us. We have no financial backing at all. Patients and doctors just send us money to help us run it. There is no charitable status because there does not seem to be any reason to ask for charitable status because we are a political campaigning group, we are completely self-financed.

97. Why do people with MS use cannabis, primarily for the relief of physical symptoms, for the

psychological effect, for the morale-raising effect of self-treatment or for all these reasons?

(*Miss Hodges*) I can speak about myself and other people I have talked to. Primarily it is for the relief of physical symptoms. In my case it is specifically for the relief of great discomfort in my bladder and my spine and nausea and tremors and cannabis has been a more efficient physical relief than anything else. Of course, when you take anything that makes you feel better it lifts your spirits. If you have a headache and you take a paracetamol you feel better, but it is not that it is psychoactive in any way. If you have any treatment that improves you, you feel better. It is the psychology of feeling better because something making you better is bound up with it. Patients do not seem to take it for any psychotropic effects. I know in larger doses it does have psychotropic effects and I have experienced that and I do not like it. Certainly to begin with, when I was feeling my way around I took too much and I had this experience of muddled thinking and I did not like it, but the amount I take now is much lower than that, enough to take the edge off your physical symptoms and, of course, you feel better as a result of that. As for the self-treatment you mentioned, I think I probably did not express myself clearly with self-treatment. By self-treatment I did not mean treating yourself outside the medical profession. We want to do it within the medical profession. By self-treatment I mean titration, you are treating yourself, you are deciding how much you need and when rather than being given a pill to take three times a day because symptoms vary and are all over the place. At the moment I feel reasonably well. Sometimes I am very ill. I need different amounts. At the moment I am not using very much, I do not need very much. That is what I mean by self-treatment and that is very important in managing the condition efficiently in my experience and in other people's experience. For the first time people feel they have some kind of control over the symptoms that seem to control you.

98. The BMA report says: "It is somewhat paradoxical that cannabinoids are reported to be of therapeutic value in neurological disorders ... since very similar symptoms can be caused by cannabis itself ... it is not clear how much of the reputed effects of cannabis in motor disorders are due to psychoactive or analgesic effects." Have you anything to say about that?



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Chairman *contd.*]

(Miss Hodges) I know that in large amounts cannabis can make you very uncoordinated and clumsy rather like multiple sclerosis can and in large amounts it can make you very heady and drunk. I have experienced that a couple of times and I do not like it, so I do not do that. That is not why I take it. The reason I took it was to help my physical symptoms. I was not using cannabis before. I had multiple sclerosis for nine years before I even tried it. This was very much as a last resort. I did not feel any need to have any psychoactive help. I needed some physical help and that is why I took it and I found not only did it relieve my physical symptoms, it generally improves my whole well-being. It does so with others as well. I think we feel why cannot we be helped, why cannot this be approved? This is why it is wonderful that you have all taken it so seriously.

(Professor Wall) There is clearly the hugely important issue of dosage and in much of our discussion this morning we will be continually referring back to the experience with narcotics where patients, in the case of treating cancer pain, exactly as Clare Hodges said, like to titrate themselves down to a bearable level of pain without muddled thinking. Patients do not like muddled thinking and, of course, huge doses will knock people unconscious, but that is not the point of therapy. So I think the indications are, from what we are listening to, which is called "folk medicine", if you like, very very reminiscent of that, that these people are talking about a very controlled careful dosage which produces symptom relief without muddled thinking.

(Mr Mitchell) I have looked through the correspondence that the ACT has received and I have had a large amount of correspondence myself. I think it is clear from those letters that it is very difficult to separate the physical and the psychological. They are turning to cannabis for relief from the symptoms particularly and they are largely concerned with people suffering from multiple sclerosis. Word has spread that it is a relief in treatment of the symptoms and they turn to it sometimes with the concurrence of their doctor, sometimes just because they have seen it in the newspapers and it has been much discussed and it is now becoming part of the atmosphere. They do feel a sense of relief. It could be argued that there would be a feeling of escapism if they just got drunk, if they turned to alcohol. That is not what they are about. It is actually a treatment of the symptoms of the disease that they are turning to it for. That means they have to be fairly calculating in what level they are going to take. This is not a pleasure drug or an escapism, it is for them a form of treatment.

(Miss Hodges) My Lord Chairman, could I just say that I think the physical benefits are measurable. Sometimes I spasm or shake and the effect is measurable. The effect it has had on my bladder is very different from how it was six years ago. It has very clear benefits. It is not just a general feeling of being a bit better, it has very clear tangible physical effects in relaxing your muscles so you do not feel so stiff and tense. A lot of the time I have to concentrate very hard on just moving and getting around and functioning. I have to concentrate very hard on how I move. Cannabis helps my body relax. I function and move much easier. The physical effects are very clear. It is not just a vague feeling of well-being. When I feel

released from having to concentrate all the time on moving, of course I feel better, I feel like I enjoy life more, I am not having to think all the time if I am going to fall over, am I going to cut myself, bang my head, bump into things.

Chairman

99. Professor Wall, is there any evidence from basic research studies that cannabinoids have an anti-spastic activity?

(Professor Wall) Yes. I like the way that your questions are running. We are talking entirely about possible therapeutic uses of cannabis and not other effects. So, yes, there is very active basic research going on on the action of cannabis and various subfractions. It is particularly concentrated on pain, because that is obviously an important issue and on such matters as you mentioned such as the motor movement. On the pain issue, it has become perfectly obvious that in animal experiments that cannabis and the cannabinoids are analgesic. However, as you will see in some of the reports that are being presented to you, they are not very strong and are at about the level of codeine. You may very well say, "If it is codeine, why not use codeine? There is nothing wrong with codeine." The interesting thing here is that there are a series of pains which are simply not well treated by any available medicine and those are really the pains of nerve damage and one could add in addition that pains of inflammation are also not really very well under control. So it is not just about seeking another analgesic similar to aspirin or morphine but looking for analgesics which will attack these particular problems for which we do not have an adequate drug. There are two very optimistic experiments in progress at the moment. One is at St Mary's where they have been looking precisely at bladder inflammation in anaesthetised animals where the whole process appears to be affected by quite moderate doses of anandamide, which is one of the naturally occurring cannabinoids and here there is a surprising effect, rather optimistic and from Germany a specific study of one of the nerve damage pains, again in animals, being affected by cannabinoids. This is encouraging.

Lord Butterfield

100. One of the reports has indicated that cannabinoids may be useful in phantom pain in limbs. Would that fit in with your interest in the damaged nerve?

(Professor Wall) This is the classic extreme example of nerve damage pain. The reason for the phantom pain is that the major nerves to the missing leg are sitting there in a highly abnormal state.

Lord Walton of Detchant

101. Is there any experience of the use of cannabinoids in causalgia, for example? What physiological explanation can you give for these preparations having any effect upon bladder control? Is there any scientific evidence suggesting that they influence the autonomic system, for example?



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Walton of Detchant *contd.*]

(*Professor Wall*) You ask two interesting questions there. The specific model that I mentioned of nerve damage is the nearest approach in animal models to a state of causalgia. It has all of the characteristics of on-going pain sensitive to the sympathetic system itself. Now you ask what might be the action of these. You understand I am not going to be able to tell you the answer to that, but I can say that work is going on and one knows what work should be done. You have read that what has appeared is that there are two quite separate groups of receptors for these cannabis drugs. One group is present in the brain and also on the terminals of peripheral nerve fibres, that is the receptor type one; and receptor type two is hardly present at all in the central nervous system but markedly present out in the periphery. That brings up the first question of whether we are talking here about an action on the central nervous system, including perhaps the autonomic system, or are we talking about action in the peripheral tissues? Of course, it could be both. When you think of the strong stories that we have been hearing about therapeutic action, glaucoma, asthma, nausea, bladder, all of those actions could be actually in the periphery, on blood vessels, on the sympathetic system and so on and this is one of the major questions at the moment. In the case of this work of Andrew Rice at St Mary's, they actually think they are looking at a peripheral action of the development of inflammation. This leads on to questions you will be asking me about whether one could separate central actions from these therapeutic actions. It is an exciting period and one does not know the precise answer to your question, which is the most important question for the scientists, but there are ways of finding out.

Lord Winston

102. The analgesic effects we are describing, do these occur before the more psychoactive effects, the feeling of being stoned, for example?

(*Professor Wall*) In some ways Clare Hodges is precisely the person to answer that. She does not like getting stoned, as she has told us, it disturbs her life.

(*Miss Hodges*) I feel that when you are ill your overwhelming motivation is to get better and to be as well as you can and I am as well as I can by taking a small amount. I have experienced this stoned or high feeling or whatever and I do not really like it, to be honest. I do it on my own. What fun is it? I have got two young kids. I want to function. I want to get up, make the tea, converse with them and be alive rather than concentrating on whether or not I have got to go to the toilet. I am not interested in getting stoned. It is not the object of the exercise at all.

Chairman

103. Can we perhaps come back to the question of natural cannabis and the problem with that as opposed to the cannabinoids. I understand the Alliance wants medical preparations of natural cannabis to be made available on prescription. What sort of preparations would they be and who would make them available? How do you see exempting

cannabis from the usual procedures for licensing medicines? Would the benefits of self-treatment be lost, particularly since doctors are unlikely to be willing to prescribe cigarettes?

(*Professor Wall*) That is a large number of questions. Shall we start first with the question since there are pure synthetic single molecules available, why not concentrate on those, which is in fact one of the conclusions of the BMA report. There are a series of such molecules available. Cannabis itself is a mixture of a number of active compounds. Have the active components already been extracted, synthesised and made available in pure form? You have a paper in front of you and Dr Notcutt has tested a number of patients by giving them the available pure cannabinoids, patients who were reporting an effect of cannabis. Not one of them said that Nabilone was as effective as cannabis. That really is anecdotal. You may say, "Well, they would say that, wouldn't they?", but all the same, I think it needs to be taken into account. Certainly I am not saying cannabis is superior to any of these alternatives. That is precisely the sort of question that needs testing because it is quite possible that cannabis contains a mixture of compounds which act synergistically. We know that there are two major routes of action of cannabis. It could be that they are working together. Again going back to the narcotics example, opium contains a mixture of effective compounds, not just morphine and it is still widely used as Omnipon which is a mixture of the compounds from opium. All that we are saying in pushing for cannabis is it would be premature at this stage of our knowledge to say, "Right, we can get rid of cannabis and concentrate on one of the purified cannabinoids." Your next questions was on the method of administration. I think it is completely unrealistic to consider a serious investigation of smoking anything, including cannabis. So that is out for a number of extremely obvious reasons. Many patients that we could be talking about simply are not used to smoking. We cannot teach them how to smoke let alone all the obvious things against smoking. There are, therefore, a number of other ways of administration under investigation and, after all, until 1972 tincture of cannabis was available. That is what Queen Victoria used for her period pains. Oral cannabis is available, it has the disadvantage of slow absorption, slow onset, but serum levels can be measured. There are other methods being investigated such as an inhaled spray. Dr Pertwee will tell you about suppositories and patches are under investigation. So, yes, as with all drugs the route of administration has to be looked at.

Lord Porter of Luddenham

104. Clare, you have given us a very vivid and interesting description of your own experiences of this. Have you taken cannabis any other way than smoking it?

(*Miss Hodges*) Yes, I did. I have varied it. It depends very much. For a while I grew it at home and that was a perfect situation because I knew the strength and I could measure it much more easily and



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Porter of Luddenham *contd.*]

I took it in a drink, I mixed it with my tea and I took a regular amount.

105. Was that effective compared with the smoking method?

(*Miss Hodges*) Yes, but for different things. Often I get very travel sick. For instance, when coming here in the taxi I actually had to be sick and I shake and then you want immediate relief and smoking is the best way to do that. When I took it orally it generally improved me all round, i.e. my appetite was better, because I had a very poor appetite, I was painfully thin, I sleep better. My general health improved by taking it orally. But it is harder to quantify and I do not grow it any more.

106. Have you taken anything other than cannabis? Have you taken cannabinoids, THC or Nabilone?

(*Miss Hodges*) The only one that is available at the moment is Nabilone in this country. THC is not available to patients here. I was prescribed Nabilone and I thought if it worked, marvellous, it would stop my problems of using cannabis but I found it was not very effective and I found it did have these effects that my Lord Chairman was mentioning at the beginning. I felt clumsy, disorientated and drugged. I felt very drowsy and it did not work very well, it had bad side effects and I did not sleep. It was not nearly as effective basically, so I thought I would go back to cannabis. This is the experience other people have had. Patients have written to us who have used Nabilone. With dronabinol, nobody in this country has been prescribed that, but I asked our sister organisation, the Alliance for Cannabis Therapeutics in the States their experience and I found the same thing with dronabinol, it is not as effective as cannabis and apparently it is very psychoactive. Patients report they get very anxious with dronabinol. That is anecdotal but it is worth passing on.

Lord Nathan

107. In preparation for this enquiry I made some enquiries into what the position was in the 19th century and I learned from that that there were then perceived to be quite different sorts of cannabis. There was cannabis, for example, from India which was very effective to produce a high, whereas what was produced in Western Europe was quite useless for that purpose. Likewise, we were told in evidence that there is no consistency as to the chemical content of cannabis grown now. We were also told that 10 or 20 years ago cannabis was far less potent than it now is because it has been grown with a particular purpose. That being so, your answers have related to cannabis as if it were one product. Could you help us as to how we should look at that?

(*Professor Wall*) This is a particular issue for people such as Clare Hodges who are, because of this paradoxical situation, forced on to an illegal black market to obtain cannabis of unknown strength, although that is changing. For example, in Holland there is a company called Hortapharm which has for some ten years now been breeding and analyzing specifically the compound so that at least now you can get cannabis with consistent properties and a

consistent mixture. Otherwise there was a quite hopeless situation. The same applied to resin and leaves and so on. Everything wrong with the word herbal could be applied to cannabis, but fortunately I think those problems are solved.

108. Clare Hodges was mentioning that she grew her own and it was a very good crop. Would you say that your crop was consistent within itself, because the evidence we received was that it was very difficult to ensure consistency even in one crop grown by one person?

(*Miss Hodges*) I got quite good at this. The smaller leaves were better than the bigger leaves. It is an interesting question about different strengths of cannabis because patients are pretty inventive because everyone recognises this and you work out how to do it. A lot of people grow it and you can buy these seeds perfectly legally and you can decide the strengths. I buy it through a friend who gets it for me. He is Jamaican and they find it very easy to get hold of. He assures me that the type I get is of very low quality, in fact. It is not psychoactive anyway, and this is what suits me fine. He said there are lots of more strong ones on the market, skunk or whatever, and I said I am not interested, I do not think that suits me. This is what helps me. I think other patients work it out. Some people find it awful. Yes, I think it is a real problem, as Professor Wall says. That is why we want a standardised dose, so that we know what we are doing rather than shooting in the dark. I am surprised that more people do not have more problems actually because of this.

Lord Dixon-Smith

109. We have also had evidence that individuals react differently to the same dose at different times and in different circumstances. Is that a problem too? We can only have the greatest sympathy with you in your predicament, but presumably you smoke it until you feel you have had enough and then you stop. Does that vary with circumstances or do you smoke a given amount once a day or whatever?

(*Miss Hodges*) It varies as much as my multiple sclerosis does. I do take it orally as well, but I did not smoke it at all really to begin with or hardly ever and now I do more. I think it depends on the problem and that varies enormously. Sometimes I am quite poorly and sometimes I am okay, and sometimes I need immediate relief for a great discomfort or sometimes I cannot get hold of it. It varies for all sorts of reasons. I cannot get a consistent dose under supervision which is what I would like. It needs some kind of self-medication along the way. It needs some self-titration. With the inhaler spray there is some kind of patient control over it, is there not? I think with something like multiple sclerosis, because it is so variable from patient to patient, so variable within the same patient, even within a day you have to have some control over your medication, I think, it is just preferable, like with pain control, I understand.



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued

*Lord Butterfield*

110. I am sure all of us regard your presentation with great admiration and we are very grateful to you for being so frank with us about how you have been conducting your personal and important trials. In the 1920s and 1930s digitalis was really a herbal medicine and the MRC, the Medical Research Council at their laboratories in Hampstead had a great lot of digitalis to which they were adding new samples so that they were diminishing the rate of change of the material that was going on to the market. I wondered whether you or any of your colleagues in your Association had used a similar kind of method of getting quite a little store together and taking some out of it and adding some to it so that there were not major fluctuations in the amount of THC in the samples.

(*Miss Hodges*) That is an interesting suggestion. I have never tried that and I have never heard of it, but it is a very good suggestion.

111. You would go out with a pair of scissors to your tomato plants, and cut off a bit of cannabis and that would be what you would be using for that idea.

(*Miss Hodges*) That is a very interesting idea. I have not thought of that, but that is an interesting suggestion. In a way I hope that someone else would do that. I feel I have got enough problems with having to provide my own medication. I think it is a great idea, but I do not think it is my place to do it.

*Lord Walton of Detchant*

112. In carrying out clinical trials of any new medication it is usually necessary to have a defined product which has been analysed and which has been tested systematically in order to identify that it is giving not only consistency in its content of the active agent but it also is producing consistent blood levels if taken in an appropriate level of dosage. One can see that being done with Nabilone or dronabinol as synthetics, but where we have difficulty is in trying to understand some of the evidence that has been given to us about the enormous variability of natural cannabis, whether smoked or taken in the form of a resin or eaten, or in whatever way it is administered. I was somewhat surprised to hear Professor Wall say that the problem of getting a consistent natural product has been overcome, because a lot of evidence that we have had suggests that may not be the case and we have been told even with Nabilone or dronabinol there has been evidence of a three- or four-fold variability in the rate of absorption and the level of the active agent in the bloodstream. How much more difficult, therefore, is it likely to be to get consistent levels from a natural agent; we would love to know how you feel that that can be overcome because it would not be difficult, once you have got a very well defined natural product, to carry out a cross-over trial comparing that with Nabilone and comparing it with a placebo. What plans might you have to try to pursue that?

(*Professor Wall*) I am not myself engaged in research on cannabis but others are. You raise a series of questions. One is the product itself, how uniform is that. Apparently these cloned cannabis plants are extremely consistent not just in terms of one factor, like the THC content, but in terms of

others these really are uniform. The second matter was about absorption. Of course, that is going to be variable. Even if you start with a genuinely uniform compound absorption is going to be variable. It is going to be variable by any route. The third question is sensitivity of the particular patient. Intravenous narcotics to produce pain control in post-operative patients with an identical operation, vary by a factor of ten in the serum levels which you need to reach for adequate pain control. So, yes, the variability of the source can be controlled. The variability of uptake is going to be a problem with any medicine and is controlled by measuring serum levels which are possible. Variability of the patient response is the whole basis of the problem of clinical trials.

*Lord Winston*

113. Would you not agree that this is a problem with quite a few drugs, it is not just cannabis? I am thinking, for example, of the gonadotrophins which have been injected into patients for a very long time and they are biologically derived and they vary hugely in their potency from patient to patient and from the same patient from month to month depending on the batch they come from. This is not limited to something which is derived from a plant, this affects animal proteins as well which can vary in their structure in ways that we do not fully understand?

(*Professor Wall*) Sure. I would like to go back to the example you mentioned of Digoxin. Digoxin is a dangerous compound. It has a very narrow therapeutic window going from the effect you want to frankly toxic effects. We are speaking here about cannabis/cannabinoids in a negative atmosphere. These tend to be treated as deeply dangerous compounds. I think that is something of an exaggeration; in other words, the therapeutic window between just having an effect and having a strong psychedelic effect is relatively wide. Here I am saying one has to act carefully with step-by-step responsible measures, but I would imagine that the huge folk experience of cannabis suggests there would be a fair range in which to explore before frankly toxic dangerous situations were encountered.

*Lord Porter of Luddenham*

114. Professor Wall, you have referred to Hortapharm in Holland and the fact that this is being developed in Britain now, cannabis with assayed potency. How is it assayed?

(*Professor Wall*) They carry out an infrared spectroscopy, picking out many compounds, not just the THC, although that is the particular aim of the thing.

115. Potency for pain relief or psychedelic potency?

(*Professor Wall*) No. What is measured is chemical content with THC being the marker chemical.

116. So it is not a level of potency then, it is a measure of a chemical compound, is it?

(*Professor Wall*) You are strictly correct but the chemical levels are directly related to the potency.



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued

*Lord Soulsby of Swaffham Prior*

117. If we could come to long-term use and tolerance. As you are well aware, the BMA report suggests tolerance does occur and that takers may suffer adverse effects. Do you have any evidence on these points, or are you concerned about tolerance?

(*Miss Hodges*) People I have talked to have not been aware of this. I know studies that have been done which do show tolerance and bad effects, which I am sure exist, have always been done on recreational users. I am not aware of anyone doing any studies on therapeutic use and the effect of tolerance or negative effects. My feeling is I think tolerance and adverse effects take on a different meaning in a pathological context. I am not aware of any tolerance on my part or adverse effects. If there was, I feel I have had six very good years relief of multiple sclerosis and if it turns out I have to take more, which I have not so far, so be it, that is part of taking medication when you are ill.

(*Professor Wall*) I think it is important to emphasise, you [*Miss Hodges*] have been taking approximately the same amount over a six year period.

(*Miss Hodges*) On the whole it has been the same amount. Sometimes I take very little.

118. In view of the great variation of effects on different people that we have heard about, it may be in your case this tolerance is not occurring, but what about other people, do they have to take increasing doses to achieve the same effect?

(*Miss Hodges*) I am not aware of that. I have never heard people say that. I think people would probably say because it would cost them more money, if nothing else. People would be aware of the tolerance, but no one has ever written and told me that. I am perfectly prepared to believe that there are such people but I have no evidence on that.

119. When you stopped using it for a while, did you return to the levels that were adequate before, or did you need to increase the levels?

(*Miss Hodges*) I am not sure I can answer that. I have not calculated that when I have had periods away. I think it is pretty much the same. I am not aware of any great increase or decrease. When there have been periods when I have not taken it I just seem to revert back to what I did before. The level that I take has been pretty consistent because I have used very much the same strain of cannabis because I have been able to do that. The friend who can buy it for me always buys the same—you do not know, it always seems to be the same kind of material. I think other patients have to work it round themselves. A lot of them grow it themselves. Different leaves vary in different strengths but basically it is the same plant.

120. Professor Wall, is there any evidence in animal experiments of tolerance developing?

(*Professor Wall*) Yes, animals develop tolerance to high toxic doses of these cannabinoids and show some withdrawal symptoms. However, I would like to emphasise that there is a world of difference between problems of tolerance and addiction, as is obvious with narcotics used for social reasons versus the therapeutic use of narcotics. This was one of the revolutions that took place 20/30 years ago. Up to that time, yes, it was assumed that narcotics were extremely useful for one or two or three doses, but if

you wished to prolong this there would be such an escalation of dosage that you would immediately get into a toxic range and be producing addiction. This is precisely what the Hospice movement investigated. They showed that if you were using a narcotic strictly for pain control, not to knock the patient out let alone any other effect, then astonishingly once you discovered an effective dose it remained stationary for long periods of time, weeks, months—I am speaking about cancer patients. Only when their condition deteriorated was an increased dose required. The development of tolerance of a narcotic for pain control is simply not a practical problem. There is a contrast between the social addiction to narcotics and their therapeutic use. It had been noticed that cancer patients on doses of narcotics where the pain was under control by another method, for example cordotomy did not ask for a single additional dose. There is a very exciting investigation going on now by Mr Bultitude at St Thomas' treating patients with a fortunately rare but a grim urological disease called Flank Pain with Haematuria. It is being treated with capsaicin. The patients are typically on high doses of narcotics over a year and are in serious pain. After the treatment, the pain goes away. They never ask for another dose of narcotics. Where a drug is being used for a precise therapeutic reason, and you can remove that reason, there is neither tolerance nor addiction. I would hope that this is a chance to say that what we are talking about here hopefully can be completely separated from the obvious social problems.

121. So you would disagree with the BMA assessment of this in terms of therapeutic work?

(*Professor Wall*) No, they were speaking of animal studies and are perfectly correct. With high doses, animals develop a tolerance to the toxic effects of these compounds. Nobody knows precisely about the therapeutic use, but we have accounts, as you have just heard, which sound as though there is no problem of a high ranging tolerance or of temporary withdrawal.

*Lord Kirkwood*

122. I know there can be no scientific answer to this question, the difference between therapeutic use and recreational use. Are we talking about orders of magnitude here? Is it one to ten or one to 100?

(*Professor Wall*) In the dosage?

123. Yes. Is there a feel for that? Is it easy for people to distinguish themselves whether they are taking a therapeutic or recreational dose?

(*Professor Wall*) Here you have an expert!

(*Miss Hodges*) Yes. I do not know what the relative doses are. In a way I am rather naive about it. I have very limited experience outside myself and the correspondence and I have virtually no experience of recreational use, so I do not know what quantities people take. But, yes, if I am feeling ill, if I am feeling stiff and I am having problems with my bladder and I take something my body functions better and I am not so uncomfortable or stiff or I can walk better and I do not need to take more and more so I get muddled and stoned or whatever. I regard that as medicine.



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Kirkwood *contd.*]

124. The whole issue, as I understand it, of whether one becomes tolerant to this or not is the dosage level.

(*Professor Wall*) It is also the aim.

*Lord Butterfield*

125. Professor Wall, as the Editor of the journal *Pain*, we are obviously very anxious to have your personal assessment of the usefulness of cannabinoids in pain control.

(*Professor Wall*) Yes. I have already answered that to a certain extent in terms of animal studies. This is now an extremely lively field going on in universities all over the world and in pharmaceutical companies. Precisely what the pharmaceutical companies are doing, of course, one does not know, except that they are clearly very busy because of the appearance of new molecules from the pharmaceutical companies. That is the amount of evidence. Animal trials are important, they clearly have to be carried out. There are very specific human problems with pain which you cannot simply translate from animal to human and, of course, this is exactly why we are here and what we are discussing is the need to make that step and hopefully to facilitate that step of studying in humans.

126. Professor Leslie Iversen very kindly went over on our behalf to a conference about all of this in New York and he came back and told us about the work of Elliot Garnier at the Albert Einstein College of Medicine in New York. It appears—this is linking up with the whole question of mode of action—that THC might exert at least part of its rewarding effects indirectly by promoting release of opiate-like chemicals in the brain. Does that appeal to you as a possible explanation of the mode of action?

(*Professor Wall*) Yes, I am aware of that work. The brain is a spectacularly coordinated mechanism which is using every means to achieve its ends and there are always interactions between the various systems. We are not dealing with the pain mechanism as though it was a fire alarm system tacked on to the brain as an isolated system. Of course, there are interactions. If you make an animal tolerant to cannabis, is it not tolerant to narcotics? There is some interaction between cannabis and narcotics but they use separate mechanisms.

127. So there are quite a lot of interesting things that might arise if we could do more research in this field to find out if people who have been on cannabinoids were more or less sensitive to opiates. I would like to warn you that having seen you in the flesh again, I am going to write to you because when I was a student with David Whitteridge I did some work on pain and I became very interested in the central summation of pain and I was going to ask you if anyone is doing any work on that aspect of pain with THC or anything like that. But I think I will return to the text! Do you want to say anything else about that remark on Dame Cicely Saunders' work showing that you could actually produce quite standard doses that would go on? We obviously have been very interested in the parallel that you have drawn between that and the cannabinoids.

(*Professor Wall*) Yes. I think it is important not just to draw technical analogy between the possible use of cannabis, cannabinoids and narcotics but to the atmosphere in which she was fighting, the social atmosphere, the medical atmosphere. When she began in the 1940s she was simply horrified by the lack of not just personal care but lack of medical attention being paid to dying patients and she realised that narcotics were useful, but useful for what? Certainly as a medical student at that time I was told, "Morphine is spectacularly useful for acute rapid onset pain which you hope is not going to be prolonged. If you persist in giving narcotics you will kill the patient." So there was this general attitude that morphine must be reserved for emergency purposes and that anybody who was seen giving morphine/heroin for prolonged times to a patient was really politely executing them. Dame Cicely Saunders entered that field with her particular moral/ethical approach and with Robert Twycross examined this and showed that the escalation does not occur. Far from killing the patient, they clearly prolonged their lives. It is an interesting moral story but it took a fight to extract narcotic use as an analgesic from a generally negative social attitude to narcotics which was growing at the time. I am not saying the outcome is going to be the same, but she recognised a very similar general social situation about cannabis and its possible therapeutic effects.

*Lord Porter of Luddenham*

128. That really leads on to whether the analgesic effects of cannabis or cannabinoids can be dissociated from their psychoactive effects. There are several ways of dissociating. Suppose the ambition was to have the analgesic effects without the psychoactive effects, that would be a reasonable ambition. If that were the case presumably it would just become another medicine, another drug and it would go through the testing and legal procedures, of course. So if we could do this dissociation that would be fine. If you are going to look at several cannabinoids or different extracts from cannabis, how do you test the psychoactive effects, for example?

(*Professor Wall*) I think there are two answers to your key question. One is that people have been attempting for 150 years to separate the psychoactive effect of narcotics from the analgesic action. It is a piece of black humour that the Bayer company produced heroin around 1880 with the advertisement that it was not addictive. For narcotics, in spite of lots of important results on the biology of narcotics, the fact is in practice there has been no separation between the psychoactive and analgesic action of the narcotics except in terms of dose. That is one answer. So it is possible that the same might apply to the cannabinoids. We do not know. You have heard, though, from Clare Hodges and we know from morphine that it is possible to separate the action of a drug depending on the dose level. If you increase an analgesic dose of morphine it would have a psychoactive effect. You asked how we test this. That is what clinical trials are all about, and they have really become quite sophisticated. There is a placebo



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Porter of Luddenham *contd.*]

action by itself and there is a placebo action associated with every active drug. It is not either is it active or is it a placebo action; something which is active induces a placebo response. Dr Henry McQuay and his group at Oxford have been looking at precisely this question, "how to carry out an analysis of patients' responses in order to separate the suggestion from the true action". We have not only the problem of narcotics but antidepressants have a separate analgesic action and it is hard to separate. These drugs were developed as antidepressants and then it turned out there was another analgesic action. This is a major use for precisely one of the diseases Lord Walton mentioned, causalgia. So it is not that people are going to stumble here and get confused, because it is possible to analyse quantitatively the shift of thinking of the person and separately the shift of the pain response. I will not go into it but it is a very serious matter with all medicine and particularly something like pain, where you might say it is all in the head anyway—I think wrongly—but where people have of course been suspicious of any analgesic medication and asked if it was simply shifting the way of thinking? Well, shifting the way of thinking is not all that simple, and one is looking here for a satisfactory-to-the-patient therapeutic effect, clear of side effects, et cetera. Out of intellectual curiosity you then want to know, have you simply made the patient say they are not in pain, or are there other indications that you are in fact affecting the pain?

129. Are the receptors likely to be different for the two effects?

(*Professor Wall*) One of the big surprises about the internal receptor is how enormously widely distributed it is. It is present on some of the control mechanisms for pain, for example substantial gelatinosa of the spinal cord, but it is also present on basal ganglia, and it is one of the most widely spread receptors in the brain, wider spread than the narcotic receptors. It may be possible to separate the psychedelic effects from the other effects on the basis of receptor type. The ideal way for that would be if it actually turned out that the action you are interested in is on peripheral tissue, in which case it would be relatively easy to find molecules which did not penetrate the blood brain barrier and did not get into the brain at all. That is one of the approaches of interest to the drug companies.

*Lord Walton of Detchant*

130. We have already talked a good deal about the potential advantages and disadvantages of natural cannabis as distinct from the cannabinoids. Can I clarify one point? When you talk about it being possible to assess the blood levels produced by natural cannabis, presumably you are not measuring the whole variety of different cannabinoids, you are just measuring the THC?

(*Professor Wall*) Exactly.

131. Secondly, in what way would you hope that future trials might be mounted? Would you prefer that if one was to use natural cannabis it should be compared with THC or dronabinol or Nabilone? How would you prefer it to be administered in such

a trial? Would it be best administered either by capsule or by a suppository or by inhalation?

(*Professor Wall*) You are certainly going beyond my expertise, but I think just a commonsense answer is convenience and an ability to reach given serum levels, and that such matters as suppositories, which the Aberdeen Group are moving towards, and inhalation would have the advantage of more rapid onset, et cetera. I am afraid they would have to be tried. My ideal would be a patch for skin absorption.

132. Such evidence as we have had from other sources has indicated that perhaps the most consistent blood levels have been produced by suppositories, but even then there is a threefold variation between individuals, and some people do not find that as acceptable as other methods of administration. When Mr Mitchell spoke in the House of Commons in January he said, "We need research into a form of cannabis that will dissociate treatment by the drug from its leisure uses." I am not quite clear what he meant by that.

(*Mr Mitchell*) It is an ultimately important and basic principle which we have constantly tried to emphasise, which is that this is not an argument for legalisation or decriminalisation or whatever, and I wanted to dissociate these two cases completely because each complicates the other. If you have, as we have now, and I have correspondence on cases in my constituency, people being arrested who are using cannabis for its therapeutic value for multiple sclerosis, it is bringing the law into a certain amount of difficulty and disrepute because the police are either cautioning or the courts are giving very lenient sentences and the whole thing is getting very difficult. It also, of course, is difficult to carry on an effective war against drugs if these people are on the frontline. The argument over legalisation also has repercussions on research because it makes research very difficult. When cannabis was moved from Schedule 2 to Schedule 1 in the early 1970s, I do not know why it was moved, I do not know what research was done, but that was a statement that the drug had no therapeutic value, which turns out not to be correct, so it would be interesting to know why that decision was taken and what kind of pressures led to it, because it was in my view, in our view, a mistaken decision. It makes research now very difficult. The drug companies are not going to take up research and they are the main providers of research, they spend most generously on research and put a large effort into it, and they are not going to take up research in this area. It is very difficult to get projects authorised. There are 19 licences issued by the Home Office and to a certain extent that is only after the kind of pressure which has been applied to get more research done. They are all laboratory research, I think, whereas what we need is clinical trials and it is difficult not only to get permission from the Home Office to use the materials but also through ethical committees, because ethical committees will run a mile rather than authorise any research. They are obviously concerned with the legality, with their reputation, and all the other factors, but in the present situation it being a Schedule 1 drug rather than a Schedule 2 drug where research could be done makes it very difficult indeed to do research. So the



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Walton of Detchant *contd.*]

argument is that we need to put it on a Schedule 2 basis which will allow research and encourage research, but encourage clinical research as well as laboratory research which is being done now. It will be research on the effects, it will be research on the basis which we want to establish, which is prescription on the named patient basis for treatment of multiple sclerosis. It is only in that way we are going to be able to reach a verdict on its relevance, its support and usefulness.

133. So you would hope to see many more research projects using a well-defined preparation of cannabis in order to study its potential therapeutic effects under Home Office licence?

(*Mr Mitchell*) I think there has to be more research. That is true of any other area and I think research has to be made easier and it has to be clinical research as well.

(*Miss Hodges*) Even if it is Schedule 2, it would still be illegal, it would not mean legalising it in any way, it would not condone its wider use. It would just mean making it like heroin, diamorphine, cocaine, which is used sometimes. Making it Schedule 2 does not entail legalising it in any way.

(*Mr Mitchell*) I think it is important to make the distinction. That it is moving Schedules, not legalisation.

*Lord Porter of Luddenham*

134. In spite of what Mr Mitchell has said, this differs from what you said, Professor Wall, because you said there is now intense activity in the pharmaceutical industry in this area.

(*Professor Wall*) I really meant on the neuro-scientific basis, not at all on the clinical level. These compounds are not being pushed towards clinical work, but they are saying, "Here is a very exciting whole new fraction of brain control being revealed which would surely become something both therapeutically useful as well as intellectually interesting."

135. And you feel the pharmaceutical industry is inhibited by the legal situation at the moment in its research?

(*Miss Hodges*) The Alliance's dealings with pharmaceutical companies is that they approached several companies early on and one company, which I cannot name here for commercial reasons, took it quite a long way and investigated at quite a level and told me in confidence that it was too controversial, the scheduling was too difficult, it just was not worth the investment. They took it seriously, but they did not want to do it. Lord Whaddon, who sat on the committee, was a great supporter of the Alliance and he contacted others as well. But very recently, at the Royal Pharmaceutical Society last summer I met a man who is ex-chairman of a pharmaceutical company and he had tried to get a Home Office licence and had preliminary discussions with them four years ago and he had been advised not to go ahead. Recently I approached him and suggested he had another go and he tried again and in fact last week he has got written confirmation he has got a licence. In conjunction with Hortopharm he has set up a new company, which I can say is G W

Pharmaceuticals, and the man is Dr Geoffrey Guy, whom I think you will probably invite to this Committee. So he has worked through it. He said it is theoretically possible to do it as a Schedule 1 drug but enormously difficult. The legislation is workable but very daunting and offputting and nobody wants to do it, but he has gone for it and he has a licence, so let's hope something will come from that. But in general the pharmaceutical companies have not been interested, it is too controversial.

136. But would a legal change to Schedule 2 affect drastically the research attitude of the pharmaceutical industry?

(*Miss Hodges*) I think the attitudes are changing. Dr Guy said that the attitudes in the Home Office have changed enormously from four years ago, they are willing to help rather than say, "Don't do it". I think if it is a Schedule 2, certainly legally it will be much easier to import, to get licences to grow it, it would be much easier to go through the ethical committees; it will just facilitate the research. It is theoretically possible and Dr Guy has done it but I do not know whether anyone will follow because of the restrictive legislation at the moment.

137. This must be the main argument for going to Schedule 2, must it not, to help the research?

(*Miss Hodges*) Yes, to facilitate research. It will not do anything else.

*Lord Nathan*

138. I understand there are 19 licences at the moment under Schedule 1, can you give us any idea as to what is happening under those because that does not sound too bad?

(*Professor Wall*) I know, Pertwee and I have discussed this matter and we are utterly puzzled because we in fact only know of four licences, but presumably the rest must be hidden in perhaps commercial establishments, maybe even Porton Down, I do not know. We make it our business, because it is easy to know what is published, and there are no 19 sources of papers.

139. If a licence is granted, is not some detail of the licence published, or is it quite secret?

(*Professor Wall*) I do not know.

(*Mr Mitchell*) In answer to a parliamentary question, I learned how many licences have been issued. It is fair to say we have been involved in a chicken and egg argument for a long period in which people have said, "It cannot be used for treatment without further research", but then they cannot do the further research either. Now perhaps they are issuing more licences and certainly Dr Guy was on the delegation we took to the Department.

(*Professor Wall*) But his is a licence to manufacture.

(*Mr Mitchell*) Yes. That has been the prime problem. I do not know what the licences are, I am sorry.

(*Miss Hodges*) I do not think the 19 licences are in force now. What I understood was that 19 licences have been issued at some stage, and some of them are many years ago and they have stopped now. There



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Nathan *contd.*]

certainly are not 19 current licences for clinical research, although some are for laboratory research.

140. Is it practical to write to enquire what these licences are, when they were granted, what they were for and what the current status is? Are they bound to produce a reply?

(*Professor Wall*) They are often confidential because they would imply a line of research which the person would not wish to broadcast. I do not know. We are now speaking about legality and the convenience for research of shifting from Schedule 1 to Schedule 2. The reply from the Home Office would be, "Look here, there is a perfectly reasonable system here, all you have to do is fill in forms and you get permission to do this". That may be true, it is true in a way, but what we are talking about here is attitude and atmosphere. If this Committee were to say that this looks like an interesting possibility for therapeutic research and it should go ahead, that might be enough. That would be an extremely important statement to move this topic out of the general negative atmosphere and make it, in a sense, respectable. The precise issue of moving from one schedule to the other, frankly, I do not think is crucial, but it would be an important signal that the decision made in 1972 that there is no therapeutic use for these things was an error and based on inadequate evidence. Now evidence has appeared, it should be shifted back again.

Chairman

141. They are still maintaining there is no adequate evidence, I gather, in the White Paper yesterday.

(*Professor Wall*) Exactly.

142. In the debate.

(*Professor Wall*) They repeated word for word what the WHO said.

Lord Soulsby of Swaffham Prior

143. Professor Wall, you have described an upsurge in basic research. You may have mentioned some of these developments as we have gone along this morning, but are there any others that come to mind which you would wish us to know about?

(*Professor Wall*) The brief answer is no. The slightly longer answer is that herbal medicine has always had problems in transition to established medicine. Opium for 2,000 years was really only used as a sedative and a psychedelic agent, which is why morphine is named for the god of sleep. It was the 19th century before it was realised that it had quite specific, separate analgesic properties. Cocaine had been used for thousands of years and in 1890 Kolle said, "By the way, this stuff is a local anaesthetic." So it can emerge from a general herbal folk use of medicine that it has specific qualities, and I think that is the stage that we are at with cannabis. Under ordinary circumstances it would just move to an investigation but unfortunately the word cannabis is associated with all the social opprobrium and there is an artificial hesitation in what would otherwise be a natural movement to investigation.

144. In the documentation prepared by Professor Iversen on this conference in New York, there does seem to be a fair amount of basic research on the pathogenesis of cannabis and on the immunology of it, getting down to the very basic molecular biological areas. Is the same thing happening in this country, either in universities or pharmaceutical companies?

(*Professor Wall*) Yes, basic work is certainly proceeding. Dr Pertwee has been one of the world leaders in developing this whole field. In the pharmaceutical companies, certainly Pfizer in the United Kingdom is evidently very busy, as is Sanofi in France and Winthrop in the States.

145. I have a particular interest in the effect of cannabis on the immune system, because it is said anecdotally at times that it destroys the immune system, but I am pleased to see Dr Tashkin from California has gone into this in some great depth. Do you have any information on that as to the basic mechanisms for the lack of production on the nitric oxide and lymph glands?

(*Professor Wall*) You realise that of these reports are based on gigantic doses for long periods of time in people who have probably all sorts of other problems as well. However, you will be receiving a report from the Royal Society and I know there will be a section in that specifically on the immune system.

Lord Kirkwood

146. I think, Lord Chairman, that Clare Hodges has already told us about the approaches of ACT to the pharmaceutical industry and what their negative response was. Is there anything you would like to add to what you have already said?

(*Miss Hodges*) Not really, just to underline that Dr Guy has taken up the challenge and he has a licence, so we have had—

147. Some response?

(*Miss Hodges*) Hopefully, very important success. It is very early days.

Lord Walton of Detchant

148. The BMA of course find it rather ironic that there have been so few clinical trials carried out on multiple sclerosis. In the same conference to which we have already heard reference, Dr Francis of McGill University in Montreal mentioned an ongoing study of 1,600 subjects with MS, comparing smoking marijuana with placebos (smoking tobacco). I do not know whether you are aware of that trial. It appears that as yet the trial has not been completed. Professor Wall, you said something about daunting and excessive controls and expressed a wish to see research facilitated. Of course as you are aware, if you have served on the Medical Research Council or medical research charities, as many of us have, first of all you have to find someone who wants to do the research and secondly of course it has to be funded. There are, however, circumstances where research is carried out specifically at the request of a funding agency. Have you any evidence, for instance, to suggest that the Multiple Sclerosis Society is

28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK WALL AND  
MR AUSTIN MITCHELL MP

[Continued]

Lord Walton of Detchant *contd.*]

wishing to sponsor any clinical trials in this particular field?

(*Professor Wall*) I do not know whether Clare can answer this but of course the Multiple Sclerosis Society lives in our society and with all this aura around the word cannabis and cannabinoids, one can see they also are not free as a charity to do that, but they are in fact making moves. Are they not appearing before this Committee?

(*Miss Hodges*) They have said publicly that if anyone applies for funds to do research, they would consider it. When we started the then chief executive said publicly they were not prepared to fund trials into cannabis but now they are very happy to do so. The tide has changed. We can see their point of view, it is very controversial.

149. But they would have no difficulty getting a Home Office licence for a well-defined trial?

(*Professor Wall*) I think there is an important issue here about funding, particularly the Multiple Sclerosis Society and, for example, the Spinal Research Trust. Some charities are committed to look for a cure, we are talking here only about symptoms control and that may be an inadequate goal for some charities.

(*Mr Mitchell*) The difficulties also remain, it is fair to say, that the research we want has not in fact been done, certainly not in this country, and that is clinical trials with registered patients who are enrolling in a clinical programme and are then prescribed preparations of natural cannabis, so they can be surveyed and monitored and conclusions can be drawn. That would probably have to be a central operation but it would solve the problem of treating themselves and it would also give us a basis of knowledge and information to reach conclusions. That is what has not been done and that is what is necessary.

(*Miss Hodges*) Can I just say, my Lord Chairman, that in a way Mr Mitchell has hit on the crux of it. What the Alliance is concerned with is the situation now. The BMA report is quite brilliant in calling for more research and it is marvellous, and if any combination of cannabinoids is found which is as effective as cannabis we would be absolutely delighted, but it would be a long time in the future and there is a problem to be addressed now and what we were envisaging or suggesting is the possibility of monitoring current users, providing them with centrally managed resources and monitoring them. That would be the kind of research we would want. It would be placebo-controlled and it would mean doctors could monitor these patients. Doctors do monitor but very informally. Most patients, certainly myself, talk to our doctors about this and they are very interested but there is no formal research. My doctor asked me what the effects were and was very interested and by word-of-mouth they are told. This would be instead of letting us go and treat ourselves in a potentially very dangerous way. If you buy the stuff illegally you could have these immunosuppression problems you have mentioned, you just do not know, but we want to see the problem addressed now as well as the research. You can do the two in conjunction.

Lord Butterfield

150. Briefly, this is going to require a major change in attitude, which you have been talking about all the time, which has been impeding research. How could trials of natural cannabis be conducted with scientific rigour? Is it that the public attitude is impeding all this, or is it something which could be achieved by regulation or some other means?

(*Professor Wall*) My brief answer to that is both, but that this Committee has an opportunity to shift attitude by making positive recommendations.

Chairman

151. A recommendation to carry out such trials?

(*Professor Wall*) Exactly.

152. Can you then answer the question, how it can be done with rigour?

(*Professor Wall*) Professor Iversen was very much in precisely this business, and of course we are talking about rigorous trials.

Chairman] I still find it very difficult to know how it can be rigorous if we do not know what we are giving.

Lord Porter of Luddenham

153. Are these trials proposed to be on natural cannabis smoked only?

(*Professor Wall*) No.

154. So natural cannabis preparations not smoked?

(*Mr Mitchell*) Natural cannabis but not smoked.

(*Miss Hodges*) There are vaporizers or patches. Professor Wall was talking about inhalation, suppositories, oral forms. No one wants it to be smoked.

(*Professor Wall*) In fact in the trial you mentioned going on in Canada, I am astonished you could have a placebo-controlled trial with smoking because I do not know what the placebo is.

Lord Winston

155. THC 3?

(*Professor Wall*) True.

Lord Winston] I cannot see the problem.

Lord Walton of Detchant

156. The trial in Canada, at least the one to which he referred, was comparing smoking cannabis with smoking cigarettes.

(*Professor Wall*) I see.

157. The crux of this issue is that we need a preparation of natural cannabis which is consistent in its content and consistent in its pharmacological effects. How we are going to achieve that, who is going to do it, is it going to be based on effort in the pharmaceutical industry or in a university department?

(*Professor Wall*) I think Pertwee surely gave you a partial answer to that question. That is exactly what they are doing.



28 April 1998]

MISS CLARE HODGES, PROFESSOR PATRICK D WALL, FRS AND  
MR AUSTIN MITCHELL

[Continued

Lord Walton of Detchant *contd.*]

(*Miss Hodges*) Can I make one point about smoking cannabis? We are not pressing for it to be smoked but, just for your information, I do not smoke it with tobacco and most people do not smoke it with tobacco, I avoid tobacco like the plague. You can smoke it with dried herbs, you do not have to take tobacco.

*Lord Porter of Luddenham*

158. Sorry, I am a bit lost!

(*Miss Hodges*) This is an aside from what we want, but when people talk about smoking cannabis, just for your information, that does not involve smoking tobacco, it need not involve smoking tobacco.

(*Professor Wall*) I do not believe that a trial would involve smoking anything.

Lord Winston] My Lord Chairman, if we have methods like spectroscopy to look at specific moieties, why can we not use those as the basis for clinical trials? I do not understand the problem, forgive me.

Lord Butterfield] It seems you need a big enough amount of stuff so you can shake it up and mix it—

*Lord Winston*

159. In a tincture or whatever. It does not seem fundamentally to be insuperable.

(*Professor Wall*) I agree.

*Lord Porter of Luddenham*

160. But is this now qualifying the natural cannabis?

(*Professor Wall*) No.

161. How could trials of natural cannabis be conducted with scientific rigour?

(*Professor Wall*) Obviously, eventually one would want to know the specific action, if any, of the individual components, but it is jumping the gun to go to the presently available individual components and assume that those are the only active ones.

162. So we are back to the question of how you have trials of natural cannabis?

(*Professor Wall*) Exactly.

*Lord Winston*

163. Would you not just give the dirty drug, knowing what it is and knowing how many variations there are in the peaks, and use that as your basis? That would still be natural cannabis, would it not?

(*Professor Wall*) Sure.

*Lord Porter of Luddenham*

164. What are they going to do, eat it?

(*Professor Wall*) Yes.

(*Miss Hodges*) I think Dr Guy is going to submit evidence and he has this in mind with his pharmaceutical company now he has the licence. He has these ideas in mind about clinical trials for the products in conjunction with Hortapharm.

*Chairman*

165. Thank you very much.

(*Miss Hodges*) Thank you very much for listening to us and giving us such a lot of time and consideration.

---

TUESDAY 5 MAY 1998

---

## Present:

Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.  
Perry of Walton, L.  
(Chairman)

Porter of Luddenham, L.  
Rea, L.  
Soulsby of Swaffham Prior, L.  
Walton of Detchant, L.  
Winston, L.

---

## Memorandum by the Department of Health

## HEALTH EFFECTS OF CANNABIS

1. The effects of cannabis preparations result from the actions of cannabinoids and of other constituents contained in the smoke on various body systems. Cannabis is derived from the plant *Cannabis sativa* and some of its sub species which contain over 400 chemical compounds amongst which 61 different cannabinoids (chemicals unique to the genus *Cannabis*) have been identified.
2. The most potent psychoactive agent is delta 9 tetra hydro cannabinol (D-9-THC). Other psychoactive compounds are delta-8-THC, cannabinol and cannabidiol. Cannabis cigarettes also contain carbon monoxide and the same tar and irritants and carcinogens that are present in tobacco smoke.
3. Cannabis is generally either smoked or orally ingested. When smoked up to 50 per cent of the compounds enter the smokestream and are inhaled. Users report that they hold their breath to maximise the absorption of THC. This also maximises the absorption of tar and particulate matter.
4. Oral ingestion will result in levels significantly lower than those achieved by smoking; this is due primarily to first pass metabolism by the liver. It also produces a slower onset and longer duration of effect but, because it is harder to control the dose of THC and for that reason, it appears that most users prefer to smoke than ingest.
5. After absorption into the blood THC becomes highly bound (97 per cent) to plasma lipoproteins and albumin. The plasma elimination half life of THC is 28–56 hours, but tissue half life is about seven days and complete elimination of a single dose from the body may take up to 30 days. THC is widely distributed throughout body tissues and there is a poor correlation between the plasma concentration of THC and its psychological or physical effects.
6. The type of cannabis grown is reported to have changed, with increasing availability of preparations with higher concentrations of D-9-THC. The assumption that this indicates higher dose consumption and possibly greater acute and chronic adversity requires further research to document its impact on both patterns of consumption and the effects of such changes in patterns of consumption.

## CANNABIS RECEPTORS

7. The science of cannabis research has moved forward significantly with the description of the cannabinoid receptors and the mapping of such receptors in the body and also, more recently, with the reporting of the existence of an endogenous ligand for these receptors. More recently a peripheral cannabinoid receptor has been identified in the spleen. The existence of the range of receptors makes it possible to further describe both the central and peripheral effects of cannabis and should significantly contribute to our understanding of the overall actions of cannabinoids in the relatively near future.
8. Central cannabinoid receptors are found in greatest density in the basal ganglia, cerebellum and hippocampus. Receptors are also found in significant concentrations in the cerebral cortex, hypothalamus, and amygdala; low levels are reported in the pons medulla and thalamic nuclei. The distribution of cannabinoid receptors is consistent with the known actions of THC and other cannabinoids.
9. The existence of receptors indicates the presence of an endogenous cannabinoid like substance. Such a substance was initially isolated from porcine brain and similar substances have been further described. The first isolate was a derivative of an arachadonic acid and was titled Anandamide after the sanskrit word for bliss *ananda*. With the description of this receptor and messenger system, called the anandamide system, it appears clear that consumed cannabinoids mediate their effect through a modification or disruption of this system. It is also likely that there are important interactions between the anandamide system and other neuroregulatory systems such as the GABA and opioid system.



*5 May 1998]**[Continued*

## TOLERANCE

10. Drug tolerance is a state of diminished responsiveness to a previously administered drug, so that a larger dose is required to elicit an effect of similar magnitude or duration. There is now good experimental evidence that animals develop tolerance to the effects of THC on repeated exposure. There is also evidence that chronic heavy cannabis smokers develop tolerance to its subjective and cardiovascular effects and evidence that some users experience withdrawal symptoms on the abrupt cessation of cannabis use. This topic has been reviewed comprehensively by Pertwee (1991).

## DEPENDENCE

11. There is clinical and epidemiological evidence that a cannabis dependence syndrome occurs in chronic users of cannabis. The risk of becoming dependent on cannabis appears to be more like that for alcohol than nicotine. Those who use cannabis on a regular basis are at greater risk of becoming dependent. This being said it is, however, clear that there is a high rate of discontinuation of daily use; studies report that of those who had ever been daily users only 15 per cent persisted with daily use in their late twenties. Kandel's work on adolescent cannabis smokers shows very high rates of medium term daily use but follow up shows very high cessation rates for young cannabis users.

12. Thus, on balance, it appears that cannabis is a weakly addictive drug but does induce dependence in a significant minority of regular cannabis users. The nature of dependence does, however, require further exploration as it is generally viewed that such cannabis dependence would have a milder clinical profile than that of some of the other drug dependencies. There is a lack of international consensus on the significance of cannabis dependence; but there is clear agreement that long term regular consumers can experience significant difficulty in their attempts to stop using.

13. There are reports nationally and internationally of requests for professional help to assist in the cessation of cannabis use, however the numbers requesting help are minuscule in comparison to current rates of cannabis use.

## ACTIONS OF CANNABIS

14. The acute toxicity of cannabis is very low. The initial effects are mainly autonomic, such as increased heart rate which appears within minutes reaching a maximum in about 15 minutes and then subsiding. This is followed by a subjective feeling of euphoria characterised by changes in perception, cognition and mood which reach a peak in about 30 minutes and last some hours. In many subjects, especially cannabis naive subjects, initial effects may, however, be strongly dysphoric with anxiety and panic attacks. Such effects may be a mixture of dose effects, background subject anxiety and expectancy. The euphoric effects are dose related and increase with dosage; but, at higher doses, may be associated with increasing levels of adverse symptoms.

## EFFECTS

15. Cannabis increases sensory perception with vivid response to sounds and increased appreciation of music. Heightened visual perception and colour perception are well described and are associated with increased appreciation of a range of visual stimuli.

16. Spatial perception and time perception is distorted. The mechanism for such changes is not clear, but THC is concentrated in sensory areas of the brain including the geniculate nuclei, superior and inferior colliculi, visual and parietal cortex.

17. Corresponding dose-related impairments in psychomotor function, especially in complex or demanding tasks, have been demonstrated repeatedly. There are increased errors, slowing of reaction time, and a specific deficit in short term memory. Impairment in motor function, including measurement of body sway, tracking ability, pursuit rotor performance, hand eye co-ordination and others, has also been demonstrated repeatedly. This may be related to the high concentration of cannabinoid receptors in the basal ganglia and cerebellum.

18. After an initial period of activation cannabis exerts a CNS depressant effect leading to drowsiness and sleep.

## RISKS OF CANNABIS

19. The health risks of cannabis have been the subject of exhaustive international reviews and debates. There are no simple answers to these questions. There is a considerable body of knowledge but there are some serious limitations in the quality of the evidence. There is a need for further longitudinal research among cohorts of heavy cannabis consumers with a good case control design if the actual adverse effects of cannabis are to be fully elucidated. Currently there are some major studies underway in the USA. There is, however, some degree of consensus on the interpretation of the available knowledge; this is outlined below.

---

5 May 1998][Continued

---

#### ACUTE EFFECTS

20. Overall, there is limited evidence of acute problems associated with cannabis consumption; the major public health issue is that of driver impairment associated with cannabis consumption.

21. On the dangers to health, the acute effects of cannabis are relatively innocuous by comparison with those of heroin, cocaine and alcohol. There is, for example, no overdose risk from cannabis and the most dependable acute effects on heart rate and anxiety are transient and reversible. Psychotic symptoms may occur but in the non-psychiatric population these appear to be relatively rare and mostly transient. Cannabis use among the population with severe psychiatric disorders does, however, appear to exacerbate symptoms, impair social functioning and increase rates of psychiatric hospitalisation.

22. To date there is very little evidence that cannabis results in increased use of other health and social services such as accident and emergency, general hospital admission or general social services. The exception to this is acute psychiatric services where data indicates that cannabis and other drug misuse and dependence may be associated with increased rates of service utilization including higher hospital admission rates and longer duration of stay, however the specific contribution of cannabis to this has not been separated out from substance misuse more generally.

23. The major concern from a public health perspective is cannabis users driving or operating machinery while intoxicated. Intoxication produces dose related impairments in a wide range of cognitive and behavioural functions including: slowed reaction time and information processing; impaired perceptual motor co-ordination and motor performance; impaired short term memory, attention, signal detection, tracking behaviour; and, slowed time perception. These negative effects are generally larger, more consistent and more persistent in difficult tasks which involve sustained attention. Studies of the effects of cannabis on road driving performance have, however, found modest impairments as cannabis intoxicated persons appear to drive more slowly and to be more aware of their psychomotor impairment. Cannabis is typically used with alcohol and the separate effects on psychomotor impairment and driving performance are approximately additive.

24. Data from the first 15 months of a three year study commissioned by the UK Government show that between October 1996 and January 1998 within a sample of 619 road traffic fatalities, alcohol—over the legal limit—was detected in 23 per cent and the next most common drug in evidence was cannabis at 8 per cent. These findings are drawn from a relatively short period of time and ought, therefore, be treated with some caution. Nevertheless, they do show a significant increase of cannabis users killed in road traffic accidents over a previous study conducted in 1985–87. Given that cannabis remains traceable in the blood for up to 30 days, whilst its effects on driving are probably limited to 24 hours at most after its intake, it would seem prudent to exercise caution over the attribution of a causal link in these fatalities.

#### CHRONIC EFFECTS

##### *Respiratory effects*

25. Chronic smoking effects are similar to those of tobacco smoking. With ongoing studies of long-term heavy consumers it is likely that a range of other effects will become apparent with time.

26. A series of studies in the United States have documented that chronic heavy cannabis smoking probably causes symptoms of chronic bronchitis such as coughing, sputum and wheezing; there is, however, uncertainty about the rate of decline of respiratory function associated with cannabis smoking. Given the documented adverse effects of tobacco smoke and the qualitative similarity between tobacco and cannabis smoke, it is likely that chronic cannabis smoking increases the risk of developing respiratory cancer. There is not, as yet, any controlled evidence showing a higher rate of respiratory cancers among chronic cannabis smokers, but chronic cannabis smoking also produces histopathological changes in lung tissue of the type that precede the development of lung cancer in tobacco smokers.

27. These effects are related to the amount smoked and not the specific effect of THC, and it is generally argued that most cannabis smokers will not smoke as much as tobacco smokers or smoke for as long in their life. This is certainly true under current conditions, legal penalties and conditions of use as shown by Backman *et al*'s longitudinal data. Most cannabis users have discontinued by their mid to late 20s.

##### *Cardiovascular effects*

28. Cannabis increases heart rate, peripheral vasodilatation and cardiac output acutely. These effects are similar to the demands of exercise and in moderate doses appear to pose no great risk to healthy adults. However, in individuals with pre-existing heart disease the increased load can carry a definite risk. The high carboxyhaemoglobin concentrations associated with deep inhalation of cannabis smoke may increase risk of atheromatous disease in long term users.



---

5 May 1998][Continued

---

*Endocrine and immunological risk*

29. Cannabis is associated with fetal growth retardation and increased complications of pregnancy and childbirth. It is, however, hard to disentangle some of the complications from other psychosocial correlates of use such as tobacco smoking, socioeconomic deprivation and related factors. There is no good evidence to date that cannabis impairs immune function to any significant extent.

*Neurological and mental health issues*

30. There is no evidence that cannabis causes structural brain damage in man. However, modern brain imaging techniques may reveal changes that to date have not been possible to study. There are some reports of persistent mild cognitive impairment after heavy usage, but the significance of such findings are not clear. There is a need for further studies on the long term effects of cannabis use on brain function.

31. Cannabis can produce a toxic psychosis at high doses, and this condition generally resolves rapidly. Given the current reported life prevalence of cannabis, it would seem that acute toxic psychoses occurs relatively rarely.

32. Heavy use of cannabis seems to precipitate an episode of schizophrenia in vulnerable individuals eg those with a personal or family history of psychotic disorder. Whilst some schizophrenic patients also report that cannabis use relieves some of their symptoms, the potential of cannabis to exacerbate psychotic symptoms and precipitate relapse is also well recognised. Currently there is no strong evidence to indicate that cannabis actually causes schizophrenia.

33. The links between cannabis use and aggression are complex. Cannabis in general decreases aggressive feelings in humans and increases sociability. However, in individuals predisposed to violence the role of cannabis in either aggravating or relieving such tendencies is not clear. Johns (1998) has proposed that cannabis use and other substance use or misuse in severe psychiatric disorders may be significantly associated with increased risk of violence in vulnerable individuals. Any discussion of violence requires a detailed understanding of the social context of this behaviour and simple cross sectional correlates of cannabis and violence are likely to result in erroneous interpretation of this issue.

34. The role of cannabis in both relieving and aggravating the spectrum of symptoms of anxiety and related mood disorders has received significantly less attention than its impact on psychotic disorders. Its capacity to act as an anxiolytic agent for some individuals and also its capacity to aggravate symptoms of chronic anxiety and depression is supported by the major psychiatric morbidity surveys in the USA and also in the UK. However, most of this data is cross sectional and there is a need for more longitudinal work to elucidate the relationship between cannabis consumption anxiety and mood disorders. Tobacco consumption is strongly associated with increasing anxiety and mood disorders and the interaction between nicotine and cannabis on such symptoms is unclear.

**MULTIPLE SUBSTANCE CONSUMPTION**

35. Cannabis use is strongly associated with the use of tobacco, alcohol and other drugs. Much attention has been devoted to the possible aetiological links of such associations. A lot less attention has been directed to the cumulative risks of chronic multiple substance consumption to both physical health and to social and psychological well-being. There is some evidence of substitution between marijuana and alcohol and marijuana and cocaine.

36. There has been limited work to elucidate the impact of ongoing cannabis consumption in reducing the capacity to achieve tobacco cessation or in the instance of heavy alcohol consumption to impair efforts to reduce alcohol consumption. Equivalently the use of tobacco and alcohol may impair efforts to reduce cannabis consumption.

37. Expenditure on tobacco, alcohol and cannabis combined may deprive families of income for broader nutritional and self care expenditure.

**CONCLUSION**

38. Overall, cannabis is now the third most commonly consumed drug after alcohol and tobacco. There is a need for an ongoing rigorous evaluation of the risks of cannabis that is conducted to a very high scientific standard in order to achieve broad credibility. One of the major difficulties in reviewing the short and long term effects of cannabis is finding the right balance. In finding the balance it seems to be important neither to understate nor overstate the risks associated with cannabis use if public credibility is to be retained and an effective public health message delivered. At the same time, because of the limited amount of cohort and case control studies, it must be recognised that the level of risk associated with cannabis use cannot be determined accurately.

*5 May 1998]**[Continued]*

39. The health effects of cannabis need to be considered independently of any consideration of the drug's legal status. The debate on the legal status does not hinge simply on the health effects but is part of a wider, and more complex, social debate.

The work presented here is a digest of international work on cannabis with particular reference to the work of Professor Wayne Hall, Director, The National Drug and Alcohol Research Center in Sydney, New South Wales and Professor Heather Ashton, University of Newcastle and refers to other key reviews commissioned by the Department of Health which will be available in the near future.

*April 1998*

## THE THERAPEUTIC USES OF CANNABIS

### INTRODUCTION

1. In the Government's opinion there is insufficient evidence to demonstrate the effectiveness of cannabis as a therapeutic agent at this stage. This is in accord with the views expressed by the BMA in their recent report "Therapeutic uses of cannabis".

2. The Government believes that it cannot accept a lesser standard of evidence in the case of cannabis than any other potential therapeutic agent. The evidence base to support the clinical use of cannabis is incomplete and consists largely of self reported anecdote. This lack of good quality evidence does not mean that the Government dismisses the potential therapeutic value of cannabis. Rather it takes the view that the scientific studies which have taken place on the therapeutic use of cannabis have not produced the necessary soundly based research evidence required to pass the stringent tests needed before it—or any other substance—can be licensed as a medicine. (The BMA report demonstrates that most of the reported scientific studies have used very small numbers of subjects and have been methodologically flawed.) This lack of reliable, well conducted research means that there is inadequate proof of the therapeutic effectiveness of cannabis.

3. The clinical properties of cannabis are thought to rest in cannabinoids, the unique ingredients of cannabis. Isolating cannabinoids may produce a long term solution to relieving the symptoms of Multiple Sclerosis and similar conditions which are not always alleviated by conventional medication. The Department of Health, together with the BMA, are looking at ways in which high quality research into cannabinoids can be encouraged.

4. Research into both cannabis and cannabinoids can take place within the existing Governmental policy and legislative framework. Both the Home Office and the Medicines Control Agency have always indicated that they are prepared to look sympathetically at well founded research proposals in this area.

### PUBLISHED EVIDENCE

5. Evidence from clinical trials of cannabis and its derivatives has been reviewed by the Board of Science and Education of the British Medical Association (BMA), the US National Institution of Health (NIH) and the UK Department of Health (DH). The BMA and NIH have published reports of their findings and conclusions. The DH anticipates it will publish a report later this year. The reviews examined published evidence relating to the following therapeutic uses:

- nausea and vomiting associated with cancer chemotherapy
- neurological disorders
- muscle spasticity
- pain
- anorexia (loss of appetite)
- epilepsy
- glaucoma
- bronchial asthma
- mood disorders
- hypertension

6. The reviewers from the BMA and the NIH summarised their findings and made a number of recommendations in relation to the scientific evidence for medicinal use. The following recommendations of both groups were similar:

- properly conducted clinical trials to evaluate the further potential therapeutic uses of cannabinoids should be encouraged.
- more basic research to discover the functional roles of the cannabinoid receptors should be encouraged to underpin their possible therapeutic applications.



5 May 1998]

[Continued

- decisions on the usefulness of cannabis and its derivatives as therapeutic agents should be based on a scientific evaluation of the relative risks and benefits.

7. The BMA noted that the information available from scientifically controlled trials of cannabis and cannabinoids in patients with various medical conditions is meagre. Nevertheless, they concluded that although cannabis itself is unsuitable for medical use, individual cannabinoids have a therapeutic potential in a number of medical conditions in which present drugs or other treatments are not fully adequate.

8. The NIH Workshop concluded that there were too few scientific studies to determine marijuana's therapeutic utility, and that more research was justified into marijuana's use for certain conditions and diseases. There was a call for peer-reviewed research by NIH to provide clear answers about marijuana's effects in the most promising applications. They concluded that the availability of delta-9-tetrahydrocannabinol (THC) in capsule form does not fully satisfy the need to evaluate the potential medical utility of marijuana because there may be other compounds in the cannabis leaf that have useful therapeutic properties and because the bioavailability and pharmacokinetics of this oral dosage form are substantially different than other routes of administration.

#### UNPUBLISHED EVIDENCE

9. Certain unpublished evidence is available to the Medicines Control Agency of the Department of Health in applications for marketing authorisations by pharmaceutical companies for medicinal use of cannabis derivatives.

10. Nabilone is a synthetic cannabinoid which is currently authorised for marketing in the UK for the indication of management of nausea and vomiting associated with cancer chemotherapy when conventional antiemetics fail. The authorisation was based on evidence of efficacy, safety and quality which was reviewed by the Committee on Safety of Medicines in 1982.

11. Dronabinol, another synthetic cannabinoid, is not authorised for marketing in the UK but is authorised in the US for: i) anorexia associated with weight loss in patients with AIDS, and; ii) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic treatments.

April 1998

#### Examination of Witnesses

DR MICHAEL FARRELL, Senior Medical Officer, DR SHEILA ADAM, Deputy Director, NHS Executive, MISS JUDY SANDERSON, Head of Policy on NHS services for the physically disabled, and DR BRIAN DAVIS, Medicines Control Agency, Department of Health, were called in and examined.

#### Chairman

166. Thank you very much for coming and welcome. Would you like to begin by introducing your team?

(*Dr Adam*) Thank you, my Lord Chairman. If I could introduce myself and our team, I am Sheila Adam, Deputy Director of Health Services in the NHS Executive within the Department of Health. On my right is Dr Michael Farrell, who is here as a Senior Medical Officer with the Department of Health, on secondment from his post as Senior Lecturer and Consultant Psychiatrist with the National Addiction Centre and the Institute of Psychiatry. On his right is Miss Judy Sanderson, Section Head within my part of the NHS Executive with specific responsibility for services for physically disabled people. On her right is Dr Brian Davis, Head of the Clinical Trials Section from the Medicines Control Agency.

167. Would you like, before we start on the questions, to say something about the Department's current thinking?

(*Dr Adam*) Thank you. If I could, perhaps, just set the context for our position, remind Members of the work which we have commissioned, and then just make one concluding statement. Our position is, of

course, set out in the paper which I know that Members of the Committee have. The legal status of cannabis is determined by the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 1985. These reflect the various UN conventions on narcotic drugs. The Department of Health has a public health responsibility to discharge, and in doing so must have an understanding of the consequences of the use of any drug, and that is regardless of whether the drug is legal or illegal. As you know, the Department has commissioned a series of literature reviews and we have informed the Commission of these. Three of the reviews, we believe, fall within the scope of your enquiry and we will be making them available to you as soon as they are ready. At the moment they are out to peer review but we hope that they should be available within the next two months or so. The three that we think are of particular relevance are on the clinical and pharmaceutical aspects, Professor Heather Ashton; the psychological and psychiatric aspects, Dr Andrew Johns; and the therapeutic aspects of cannabis and cannabinoids, Dr Philip Robson. The concluding remark from us—is just to emphasise the point that research into both cannabis and cannabinoids is possible within the existing policy and legal framework, although we do recognise that there are some perceived problems



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

Chairman *contd.*]

from the field. Both the Home Office and the Medicines Control Agency look sympathetically at well-founded research proposals, and within the Department of Health we very much recognise the importance of research in this area and its potential value, particularly when addressed to the needs of patients for whom we have relatively little else to offer. I know that that will be the focus of some of our discussion this morning.

168. We have had quite a lot of evidence from people with MS and other chronic pain who are using natural cannabis to obtain relief from symptoms, which they cannot control in other ways, sometimes with the knowledge and even encouragement of their GPs. Should the evidence of numerous patients whose stories agree continue to be regarded as anecdotal and insufficient to prove therapeutic value? If so, would you advise such patients to stop? What is your advice to the doctors of such patients?

(*Dr Davis*) I would like to address the first part of that series of questions. Should the evidence of numerous patients whose stories agree continue to be regarded as anecdotal and insufficient to prove therapeutic value? I would like to refer to the International Conference on Harmonisation. That is an agreement between the governments of the European Member States, the United States and Japan in conjunction with representatives of the pharmaceutical industry. They have agreed, as part of this conference on harmonisation, on general principles concerning the development of medicinal products for human use. One principle is that clinical trials should be designed, conducted and analysed to sound scientific principles to achieve their objectives, and should be reported appropriately. This is outlined in a guidance note from the International Conference on Harmonisation on general considerations for clinical trials. Use of anecdotal reports would not satisfy this criteria for a number of reasons, including the potential for bias on the part of the participant or the investigator in reporting the outcome of the intervention.

*Lord Dixon-Smith*

169. There is no point at which the anecdotal evidence would be so numerous and so forceful that it would be regarded as acceptable?

(*Dr Davis*) I can only refer to the considerations of a large number of experts from around the world who have come to the conclusion that for development of a product for medicinal use for humans that would not be acceptable.

Lord Winston] Would you not agree, though, that that answer could be given for any plant-derived abstract which is made for medicinal value initially? It could apply to digoxin or anything else. It still does not avoid the need for trials.

(*Dr Davis*) Referring back to the question, the question asks whether anecdotal evidence would be accepted. I would submit that anecdotal evidence, again, would not be accepted as a basis for the marketing authorisation for a medicinal product.

*Chairman*

170. If you take the historical view, these extracts have been used from time immemorial. What you are saying about the international agreement refers to new compounds, not the historical ones.

(*Dr Davis*) I would submit that in developing any new product we should use the technology that is available and has been developed over hundreds of years. I would accept that at the early stage of developing medicinal products they were developed using anecdotal evidence, but I would suggest that that is no longer an acceptable approach to developing medicinal products.

171. New products are governed by the rules you have mentioned, but there are others that were used before the rules were developed, and continue to be used.

(*Dr Davis*) I agree with that.

172. Would you advise patients to stop?

(*Dr Farrell*) I think the general view would be that we would advise that most doctors should advise patients about the existing laws and advise them about the limited evidence for the efficacy of the treatment. However, in the context of an individual doctor/patient relationship one has also to recognise that people may choose to do things that their doctors advise against, and there would be a necessity for the doctor subsequently to continue to work to support that individual. The first line of advice would be that there is not good evidence for the benefits of the treatment.

*Lord Walton of Detchant*

173. Accepting all the problems, of course, related to anecdotal evidence, it has been suggested to us from many sources that the synthetic cannabinoids, such as nabilone and dronabinol, do not have as beneficial a therapeutic effect as does natural cannabis. When we look at natural cannabis the problem there is that whatever the preparation used and however it is administered—whether by smoking, inhalation, or by the oral route—the actual blood levels seem to be extraordinarily varied between different individuals. The Alliance for Cannabis Therapeutics wants selected medical preparations of natural cannabis, which they believe to be more valuable therapeutically, calibrated so they contain a standard dose of THC as well as the other naturally occurring cannabinoids, and they want this preparation to be available on prescription. What is your response?

(*Dr Davis*) My Lord Chairman, we are not aware that a product similar to the one proposed by the Alliance is available. The development of such a product is more difficult than developing a synthetic product. Controlling the quality and potency of a natural product is likely to require more demanding controls and tests than a synthetic product. For instance, the potency of a natural product can vary considerably from one crop to another. A company developing such a product would need to provide evidence of quality, safety and efficacy for the proposed indication in the usual way before a marketing authorisation could be granted.



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

*Lord Walton of Detchant*

174. In relation to this, we would be interested to know why the tincture of cannabis was prohibited in 1971 and cannabis was placed in what is now Schedule 1. What would be the implications if it were moved to Schedule 2, and what would it take to persuade Government to do so? Do you regard the campaign for the therapeutic use of natural cannabinoids to be a front for general legislation?

(*Dr Davis*) To take part of the answer; when the Medicines Act 1968 was introduced all of the medicines that were currently available were granted a licence of right, and they then came up for review in, I think, 1973. There was insufficient evidence, or no evidence provided, to support the therapeutic use of the tincture of cannabis, and, therefore, it was not granted a product licence. One of my colleagues wished to address the information about the Pharmacopoeia. We have not got all of the evidence but we could submit further evidence on this if you would care.

(*Dr Farrell*) My understanding is that the reason cannabis was prohibited in 1971 was because of the problem of diversion of some doctors prescribing tincture of cannabis as part of the growth of the cannabis problem in the late 1960s and early 1970s. However, that is purely anecdotal, and we will seek further information on it and submit a further answer to your Lordships.

*Lord Walton of Detchant*

175. Then the question as to why it was placed in Schedule 1.

(*Dr Farrell*) I think that is a question on which we would like to consult the Home Office and come back to you with an answer.

176. The points you make about preparing a standardised preparation of natural cannabis are very valid indeed, but as Lord Winston said, digoxin is a product which is from botanical sources and it took some considerable time before that could be standardised. Is it out of the question that a natural cannabis preparation might be prepared to give a standardised dose and a standardised blood level?

(*Dr Davis*) No, it is not out of the question, but no pharmaceutical company has come forward with such a product and I was just pointing to the difficulties outlined in discussions with one of the pharmaceutical companies that is involved with this type of product. They went through a list of the difficulties in dealing with these products from natural sources.

(*Dr Farrell*) The last question you asked was whether we saw the campaign as a front for legalisation. I think we see very much the genuine concern of some people to find medicinal products for intractable conditions. We see that, clearly, there are other people who may well hide under this campaign, but we do see that societies, such as the MS Society, do have a genuine interest in the potential for therapeutic benefit, and in the Department of Health we would support explorations of potential therapeutic benefits.

*Lord Kirkwood*

177. Given the fact that many scientifically controlled research experiments still need to be done on cannabinoids before their proven therapeutic value is established, does the Department of Health feel that, at least as an interim measure, before more effective drugs are available, medically prescribed cannabis can be permitted to MS sufferers and sufferers of other debilitating diseases? Do you feel that could be an interim measure, since these people seem to feel that they get some therapeutic value from it?

(*Dr Davis*) Going back to some of the other points that I have made previously, before a product could be given a marketing authorisation there would have to be evidence of efficacy, safety and quality of the product. A major difficulty, as I have explained, is that there is no product, that we are aware of, that can be tested to give that evidence, at the moment, from a natural source.

178. These products clearly are nevertheless available and, obviously, MS sufferers do smoke the material. What I am asking is, as an interim measure, can this not be permitted as a medically permitted prescription? I am not talking about the long-term, I am talking about those people who believe they get some therapeutic response from this; that they should, under medical prescription, be allowed to take this natural drug. I am asking whether the Department of Health do not see that there is some short-term advantage in this, before going through full trials and getting through to properly regulated and controlled drug use by prescription? Clearly the stuff is available.

(*Dr Davis*) If I can respond from the point of view of the licensing authority (the licensing authority being the Secretary of State for Health, the Minister of Agriculture, Fisheries and Food, and the Ministers in Government Health Departments in Scotland and Northern Ireland, who are responsible for licensing of medicines) to allow prescription on a licensed basis, I would submit, it would be extremely difficult to make an exception without having evidence of quality, safety and efficacy, without some extraordinary basis for doing that.

*Lord Rea*

179. When I first qualified as a doctor, which was about 40 years ago, it was quite common for doctors to prescribe various forms of alcohol to help their patients. It is not quite so commonly done now—certainly not on the NHS. Although, perhaps, the effects of alcohol were more fully documented than cannabis as such, would that not be a rather similar sort of thing? If a doctor felt that a patient's symptoms would be relieved, it might be a reasonable thing for them to be able to advocate—if not prescribe it on the National Health Service.

(*Dr Davis*) There is a freedom within the Medicines Act for a doctor to prescribe to a particular patient of his or hers. That clinical freedom allows any doctor to prescribe a substance where he or she feels that there would be a benefit to that patient. At the present time, my understanding of the way that the law is constituted is that a doctor cannot do that because of the restrictions on cannabis itself. There



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

Lord Rea *contd.*]

would be nothing to prevent a doctor providing a synthetic cannabinoid that was not controlled under the Misuse of Drugs Act.

Lord Rea] I think you have made my point for me.

*Lord Dixon-Smith*

180. I cannot imagine anybody wanting to drink industrial alcohol, which might be very pure, but I can imagine some doctors having a great debate as to whether they should prescribe claret or burgundy! I do understand, if you like, the desire for the medical world, in its widest description, to have medical products that are consistent in their constitution so that you can have some certainty of outcome and some certainty of what it is you are prescribing. However, if I understand matters correctly, and given that we try very hard to work to that consistency, nonetheless the reaction of individual patients to that given, specific dose can be enormously different and, indeed, different within individuals in differing circumstances. Given that we have variability at that end, I do have just a slight hesitation about the absolute embargo on the possibility of variation at the other end. Perhaps this is why, if my medical colleagues will forgive me, they are always "practising"! That said, I am interested in your response to the BMA report on therapeutic use. Have you actually discussed it with the BMA? Do you not think that perhaps you might do something to encourage and facilitate research and, perhaps, controlled trials in the areas that they recommend? If that were acceptable, would the Department and the NHS commission research in this area, either directly or, perhaps, through the Medical Research Council?

(*Dr Adam*) We welcome the report from the British Medical Association, which is a thorough and rigorous review of the evidence. The Chief Medical Officer, Sir Kenneth Calman, met Dr Vivienne Nathanson and her colleagues from the BMA in March, and they had a full discussion of the report. As you know, we have commissioned four literature reviews, one of which addresses the therapeutic aspects of cannabis use. We shall study that report carefully in terms of looking at further actions which the Department might take. In general, the Department would not fund research into the development and testing of a new drug. That is usually funded by a range of other bodies, including the Medical Research Council, and we do have an agreement with them which expresses our relative responsibilities. However, we do recognise the distress which conditions such as Multiple Sclerosis and cancer being treated by chemotherapy cause, and the limitations of the other treatments available. We would therefore be keen to encourage high-quality research in this sphere. I think it is important to pause there and reflect on some of the difficulties in designing high-quality research. It is not only to do with refining and calibrating the substance which we would be testing; we need to think about the mode of administration and the combination of this with other drugs, because I think there is some evidence of the benefits of combining cannabis or cannabinoids with other medication. A lot of people have written

about the difficulty of clinical trials in this area, but we would be looking for large numbers and, in some cases, follow-up over a long period of time. The follow-up of patients with illnesses such as MS is particularly difficult because they fluctuate over time and we would need end points that were both subjective and objective. The gold standard of the double-blind, randomised, control trial would be difficult in terms of how you could blind some of the treatments that we might be thinking of. So we have a number of difficulties in terms of getting the research design that is going to answer the questions that we would be looking for. Research would be difficult but it would also be expensive and, as has previously been said, the contextualisation would also be very important. It is obviously different to assess the use of a drug for someone whose life expectancy is extremely limited from assessing the use of that drug over a longer period of time. Having said all that, we do welcome the initiative which has been taken by the British Medical Association, working with others. I believe they discussed this with you in their evidence to you a couple of weeks ago and there is a brief report in last week's British Medical Journal which summarises the action they are taking. I hope I have made it clear that the Department of Health would wish to do all it could to support and facilitate that initiative.

*Lord Nathan*

181. In view of what Dr Davis said in his earlier remarks, how far do you, as a group and, indeed, as a Department, feel constrained by the provisions of the conventions to which Dr Davis referred?

(*Dr Davis*) I would submit that the International Convention on Harmonisation, my Lord Chairman, is a process that has been going on over several years, with the aim of trying to agree on what are appropriate standards for the development of medicinal products in the three regions of Japan, United States and Europe and that there have been wide consultations, both throughout industry and throughout all of the Member States of Europe, including the United Kingdom. In coming to the principles that were laid down, I, personally, know that there was very little criticism of that approach of requiring a scientific approach to the development of medicinal products. In a short answer to your question, I would say that we do not feel particularly constrained by these things; they have been accepted after wide consultation.

182. How about the proposal advanced that selected medical preparations of natural cannabis calibrated to contain a standard dose of THC as well as the other naturally occurring cannabinoids should be available on prescription. To what extent would doing that, in your view, be tricky in relation to the terms of the International Convention?

(*Dr Davis*) If a suitable product was developed a company could apply to conduct clinical trials. They could obtain the appropriate licences to do that, they could develop the evidence and provide evidence on quality, safety and efficacy, and they could, in fact, obtain a marketing authorisation. The conference on harmonisation would not, in any way, impede that.



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

*Lord Porter of Luddenham*

183. I can see the very great difficulties in dealing with natural cannabis, and I would hate to have to do research on natural cannabis, because we have heard there are 400 separate components and so on. Yet the demands which we have heard expressed so forcefully are for natural cannabis. I wonder where the distinction lies in the minds of those people. It would help, first of all, if we could hear a little more from you about nabilone—and, perhaps, dronabinol—because you say, in your evidence to us, that nabilone was authorised and the authorisation was based on evidence of efficacy, safety and quality which would be reviewed by the Committee on the Safety of Medicines. Surely this implies it is an effective, therapeutic agent, and the problem then would be on safety, and so on. If it is effective, you are over one big hurdle. Could you tell us how widely it is being used in the United Kingdom and with what results?

(*Dr Davis*) Nabilone is a synthetic cannabinoid which has been shown to have significant anti-emetic activity in patients. Although its anti-emetic action is not yet fully understood, it is apparent that there are a number of points in the control systems of the body at which nabilone could block the emetic mechanism. I would like to emphasise, that is its only indication. It is indicated for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer, and that is in patients who have failed to respond adequately to conventional anti-emetic treatments. There is also a further restriction on the licence that it can only be supplied to hospitals for prescription in hospitals. There is a wide amount of information in the summary of product characteristics for nabilone, which is published and I have a copy here. If there were any specific questions I could answer them or I could supply a copy of the characteristics.

184. First of all, could you tell us, does it have a psychedelic effect? Does it give a high?

(*Dr Davis*) If I can refer to the document—

*Lord Walton of Detchant*

185. We had evidence from one source to the effect that the drug company which introduced nabilone as a therapeutic agent in the United States back in the 1970s did actually have a licence to produce it, but eventually found that its psychedelic consequences were so great that they impaired the beneficial effect of the drug and, therefore, they stopped producing it and withdrew it from the market.

(*Dr Davis*) If I could just read from the summary of product characteristics. Under "Drug abuse and dependence" it says: "Nabilone is an abusable substance capable of producing subjective side-effects, such as euphoria or 'a high' at therapeutic doses. Prescriptions should be limited to the amount necessary for a single cycle of chemotherapy—ie a few days. The physical dependence capability of nabilone is unknown. Patients who participated in clinical trials of up to five days' duration showed no withdrawal symptoms on cessation of the drug."

*Lord Porter of Luddenham*

186. In view of that, can I ask what, in your opinion, is the reason for so many people writing to us very, very convinced that nabilone does nothing for them, essentially, and natural cannabis is what they want?

(*Dr Davis*) This would only be a personal opinion, as I do not have any evidence to support it, but you may be aware that nabilone is taken orally and that the people who are writing to you are often smoking natural cannabis. The bio-availability of cannabis taken through the intestinal tract is very limited and very varied, and a much higher concentration becomes available by smoking it. It may be that patients that have some effects by smoking cannabis—

187. Can we look at that the other way round, then? Is it not possible to take these synthetic drugs, such as nabilone and so on, through smoking? Has it been done?

(*Dr Davis*) I am not aware of any product that is delivered in that way.

(*Dr Farrell*) There is no product available currently, but there is exploration within the United States and Australia on the possibility of developing cannabinoids that could be delivered through inhalation mechanisms. However, it is at a very early and theoretical stage of discussion.

*Lord Rea*

188. That would be cold inhalation, not by burning it?

(*Dr Farrell*) Well—

Lord Winston] A nasal spray, presumably, would be the mode?

*Lord Porter of Luddenham*

189. This question is very near to an important problem. You have told us that nabilone is efficacious and so on, and yet it obviously is not very acceptable to the people who suffer and say they get relief from natural cannabis. Therefore, is it not possible to bring the two together, so that if nabilone is so effective and can be shown to be safe—which it can, certainly; it is a pure substance so one can do research on it—should we not be pursuing this as an alternative for those people who suffer and find, at the moment, according to themselves, only natural cannabis works?

(*Dr Davis*) I would like to emphasise that the efficacy that was shown for nabilone was as an anti-emetic, and that was the only indication for which it has a licence. In order to determine whether it was efficacious for other symptoms—for instance, spasticity in Multiple Sclerosis—one would have to conduct suitably designed clinical trials to demonstrate that, with a suitable product.

190. Is there any reason why clinical trials should not be suitably designed? With natural cannabis I can see it is very difficult, but with nabilone, and synthetics, is there any reason why one should not have—as one does with other drugs—suitably designed trials?

5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

Lord Porter of Luddenham *contd.*]

(*Dr Davis*) No. It would be quite possible to develop a product and to design clinical trials and make appropriate measurements.

191. In view of the people who suffer from MS and the relief they seem to get from natural cannabis, is it not important that somebody should be looking at nabilone and other synthetics for efficacy as treatments for MS?

(*Dr Davis*) As far as I am aware, no one has come forward with such proposals at the moment.

Lord Porter of Luddenham] Why do you think this is? Surely they think it is important?

Chairman

192. Perhaps it is because although you categorised it as having therapeutic value and having efficacy and consistency, it still stays in Schedule 1?

(*Dr Davis*) Nabilone is not—

Lord Soulsby of Swaffham Prior

193. Could we go back to this knotty question of anecdotal evidence and rigorous evidence? Your submission is not too critical of cannabis—in fact, it almost gives it a fair wind. You might not agree with that comment. However, in view of the difficulty of getting data on the quality, efficacy and safety, would it not be possible to enrol a significant number of people who are using natural cannabis on a nationwide scale on long-term trials to try and get some evidence—anecdotal at present, but using epidemiological methods—to study this? Of course, if you did favour such trials you would have to guarantee patients' confidentiality and immunity from prosecution. It does seem to me there has got to be some large-scale evaluation of this, because we are at an impasse at present, with some people saying yes, it is valuable and others saying no. The only way to do it, to my mind, would be a large-scale epidemiological study, using all the modern techniques of epidemiology.

(*Dr Davis*) My Lord Chairman, I would refer back to the previous difficulties that I have mentioned, and that is that there is wide variability in the potency and the standards of the material of natural cannabis (which I believe you are referring to) on patients who are smoking this material. That would make it very difficult to draw an adequate scientific conclusion from such a study. In order to support the licensing of a medicinal product, in order to do adequate studies, you really would need to start with a defined product, conduct clinical trials with that defined product and then that product could be submitted for a licence.

Lord Walton of Detchant

194. Let us suppose that one could produce a standardised preparation of cannabis resin, and a mechanism be devised whereby it could be given by inhalation. If that were acceptable, surely it would be possible not to carry out a double-blind trial (which, I admit, would be very difficult) but to carry out, in patients with spasticity due to MS—one defined

condition—a trial comparing it on a cross-over basis with nabilone and a standard treatment for spasticity, such as baclofen or a benzodiazepine? Surely that would not be an impossible task, provided one got the preparation in the first place. If that was so, is it the kind of thing, that would be properly funded through the Department's own R&D initiative?

(*Dr Adam*) My own view—and I do not manage the Department's R&D budget—is that that is unlikely to be 100 per cent funded by the Department, because we focus our research more at the health service research end—the implication of policy end—rather than at the rather earlier stages of clinical trials and testing products to see whether they are, indeed, effective and cost-effective. That is not to say that we would not be prepared to consider it, obviously, and I personally, also, cannot see why such a study could not be designed and should not seek funding. On the whole, the Department does not fund towards the bio-medical and clinical end of the research spectrum, it looks to others to do that, but we have been known to facilitate and work with partnerships on such projects, and that is something that could be considered.

Lord Porter of Luddenham

195. How widely is nabilone being used in the United Kingdom, with what results, and for what?

(*Dr Davis*) My Lord Chairman, we do not have records of how widely it is used. We could explore this further by writing to the company, who could then give us that evidence, if you would like us to do so.

196. I think we would. Whilst it is almost the same question, could you tell us, or let us know, the same thing about dronabinol? I realise that is imported legally into this country from the United States for prescription to a named patient as an anti-emetic. How many prescriptions have been made for dronabinol and with what results?

(*Dr Davis*) Again, we do not have the information on that. The ability for a doctor to import a drug for particular patient use carries an automatic exemption under the Medicines Act, so they do not need to get an approval from us, so we would not have records of the number of prescriptions. Again, we could write to the company involved and ask them that information, as they are required to keep records. So we might be able to obtain that.

Lord Rea

197. Could I go on to look at the measuring of the adverse effects of the use of cannabis and ask you what you regard as the most serious adverse effects of, first of all, acute and, secondly, long-term cannabis use that might limit or prevent its therapeutic applications.

(*Dr Adam*) I think the information is limited, as the Committee knows, and is also, I think, very context-dependent. It does seem to me, in talking about the side-effects of any drug, that we do need to look at those in the context of the patient, of the symptoms that they have, at the alternative medication



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

Lord Rea *contd.*]

available and of their life expectancy and quality of life. So, obviously, that will vary from patient to patient and group to group. I think, in terms of the short-term side-effects, our reading of the literature is that these do exist but appear, on the whole, to be reasonably well tolerated. Indeed, I think there is some evidence, which the BMA report quotes, that at least some patients prefer the side-effects of cannabinoids to the side-effects of alternative medication. Obviously, there can be impairment of psychomotor and cognitive performers, which is important for those who might be driving or operating machinery, and there do appear to be particular risks in some people; one group, perhaps, to highlight, is those with a history of psychotic disorder. Would you like me to go on to the longer-term, as we read it?

198. I think so, yes.

(*Dr Adam*) On the longer-term side effects, obviously there is a question about whether tolerance develops, or dependency, and whether people do get withdrawal symptoms. Our reading of the literature is that there is quite a lot of uncertainty about that. I suppose the most important concerns around the long-term adverse effects are those associated with smoking, which the BMA Report does articulate very clearly—the whole range of lung disease and heart disease, particularly in those who are already susceptible. I would stress the point I opened with, in looking at these long-term adverse consequences it is important to view it from the patient's perspective and we would certainly wish to see that taken into account in thinking about the design of research proposals and also future prospects for therapeutic use of cannabis or cannabinoids.

199. When you say the effects on the respiratory system are similar to those from smoking tobacco, were you suggesting that the cannabis itself produces similar effects to tobacco, or suggesting that the vehicle with which most people imbibe the natural product, tobacco with which it is mixed, may actually be what is responsible for causing the respiratory damage?

(*Dr Adam*) I am going to look to my right, because I think my level of understanding is not good enough for me to give a good answer.

200. And what trials are there which would try to separate the two?

(*Dr Davis*) Briefly, it would in fact be the tar components of the tobacco where—as with other tobacco products—there is some evidence to show that it has effects on respiratory disease in reported publications.

Lord Dixon-Smith] If we are dealing with patients who have got irreversible conditions and possibly a more limited expectation of life, is there not an argument somewhere along the line that there is a slightly different standard of ethics which is applicable? It seems to me to be a very fundamental but difficult area.

Lord Winston] The Brompton cocktail argument.

Lord Dixon-Smith

201. Yes.

(*Dr Davis*) In the assessment of all medicinal products, one takes into account the risk and potential benefits, and obviously where the potential benefits outweigh the risks then it is possible to grant the licence even where there would be considerable risks, but it depends on the condition that is being treated.

Lord Rea

202. Is it possible to separate the effects of smoking tobacco as a vehicle from the effects of the combustion of the cannabis itself, on the respiratory system?

(*Dr Davis*) I am not an expert in this area, but it would be very difficult to separate those two things out on an experimental basis. You may be able to draw certain conclusions. I am not very familiar with the published literature in this area but there is published literature.

Lord Rea] I would have thought animal experiments could be done which would at least throw some light on this.

Lord Porter of Luddenham] We have been told that in addition to the two points that Lord Rea made there is another one in that cannabis smokers smoke differently. The base material, the tar and so on, are going to be the same but we were told they retain the smoke in their lung much longer.

Chairman

203. I think, from my own reading of the literature, the passion engendered about the toxic effects of cannabis is just as great amongst those who are in favour of it as those who are against it. You get articles which say that this is extremely toxic material, and there are other articles which say this has never caused a death. The point I am coming to is, is the point you made about different people reacting in different ways likely to be the same as the fact that the therapeutic response is varied?

(*Dr Adam*) I am afraid I do not have the expertise to be able to answer that question. I do not know whether anyone else feels they have.

(*Dr Davis*) Only in general, that there is some evidence of variability of response with cannabinoids and natural sources of cannabis.

Lord Winston

204. Coming on to the recreational use of cannabis, one of the interesting things was the evidence we have heard from people, using cannabis because of its perceived effect on their neurological symptoms, who are very concerned that they do not use it for recreational use. I think that is quite interesting. They do not want to get a high, for example. Can you tell us what advice you give currently on the health effects of recreational use of cannabis?

(*Dr Farrell*) We have made available to you the printed and published *Health of the Nation* which is

5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

Lord Winston *contd.*]

promoted through the Health Education Authority to young people about the health effects of cannabis, and we have a copy available and we can make as many copies available to you as you wish. Basically it is in general to advise people they need to know (a) about the effects of cannabis and (b) about the risks, and it is the risks which tend to be concentrated on. This is clearly health information for the general population on the intoxication effect, the effect on possible inco-ordination and increasing risk of accidents, the possibility of impairing driving skills, and the possibility of generating anxiety and sometimes paranoid states, and also to highlight the risks of initiating and combining it with tobacco where tobacco-dependence may also occur. We focus on the issue of the longer-term risks of respiratory problems and also point out that it may be difficult for people who regularly use cannabis to quit its use. That is the range of information that is made available.

205. Would you tell us about the scientific basis for the advice you are giving?

(Dr Farrell) In the submission to you we outlined the scientific basis for the respiratory effects on the basis mainly of some longitudinal North American studies, particularly by Tashkin, which report on the respiratory effects of cannabis. We also pointed out that there is not to date a controlled study specifically linking cannabis with cancer *per se* apart from its additive effect to tobacco. There have been numerous studies done on the motor co-ordination effects and there is a difference clearly between understanding the motor co-ordinating effects in the laboratory setting and these effects in the community setting. Clearly we are concerned in relation to the evidence that there are increasing rates of cannabis-positivity in road traffic fatalities, and we are concerned that that is indicative of the contribution of cannabis to road traffic fatalities.

206. Do you have figures on that available?

(Dr Farrell) Yes, we do.

207. Are these substances routinely tested?

(Dr Farrell) In the data provided to you, in the three year study commissioned by the Department of Transport between October 1996 and January 1998, in 619 road traffic fatalities alcohol was detected in 23 per cent and the next most common drug in evidence was cannabis at 8 per cent. As far as I understand it, all fatalities are tested for alcohol and cannabis, but I would need to check that.

208. What about the scientific basis for your advice about dependence and addiction?

(Dr Farrell) First of all, there is reasonable evidence from animal studies of the development of both tolerance and withdrawal associated with cannabis. Separately, it is not that we wish to overstate the nature of the dependence associated with cannabis but as the smoking of cannabis has become more engrained within populations in Australia, the United States and indeed the United Kingdom, it has been possible to study long-term consumers of cannabis. In particular, studies by Wayne Hall, in Sydney, have reported that in cohorts of long-term cannabis smokers up to half of them can report significant difficulties in reducing their consumption,

but they are a particular sub-group in that they are chosen because of their characteristic of persisting with daily cannabis use over many years. This has been quite important in relation to trying to understand the overall balance, and clearly these are a minority of the overall numbers of people using cannabis and the majority of people who use cannabis even on a regular basis will stop its use. The North American study, particularly the Denise Kandell studies, has demonstrated that the majority will cease, but there is a core who develop persistent and dependent use.

*Lord Porter of Luddenhams*

209. What was the figure you gave for the number of accidents in which cannabis was involved?

(Dr Farrell) It was 8 per cent.

210. 8 per cent of those involved in accidents had cannabis detected?

(Dr Farrell) Yes.

211. How does that compare with a random sample of motorists who do not have accidents?

(Dr Farrell) It is a good question.

*Lord Walton of Detchant*

212. Those were fatal accidents?

(Dr Farrell) Yes.

*Lord Soulsby of Swaffham Prior*

213. On the effects of cannabis, if you give it up and then regress and take it up again, do the adverse effects come on more quickly or is it the same rate of acquisition of adverse effects?

(Dr Farrell) If the question is in terms of the pattern of dependence and rapid reinstatement of that behaviour, in terms of human studies I do not know of data. I do not know if anybody has published any data where they have studied people who have stopped and restarted.

Lord Soulsby of Swaffham Prior] I think you have answered my question, that it is a normal progression of effects rather than any speedy additive effect.

*Lord Winston*

214. Just to get it clear in my mind, and this is a question on the bias of the sample, is it mandatory you test for cannabis in fatal accidents and not at any other time? How is the sample derived?

(Dr Farrell) The sample is obviously fatalities.

215. So all fatalities are automatically tested?

(Dr Farrell) Yes, as far as I understand it. There is a proposal at the moment to do pilot checks in roadside testing around cannabis, but I think that is at a pilot stage.

Lord Porter of Luddenhams] 8 per cent does not strike one as very high, knowing how much cannabis there is around.



5 May 1998]

DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS

[Continued]

*Lord Rea*

216. And remembering that it can persist in the blood for 30 days. Can I take you to the section in your evidence which discusses multiple substance consumption, paragraph 35 onwards? We have actually covered some of the ground, particularly with regard to joint use of tobacco and cannabis. If attention were directed to the cumulative risks of chronic multiple substance consumption, as suggested in that paragraph, what might we find which would add to our understanding?

(*Dr Farrell*) The reason I put this in is because there is a tendency to think of cannabis consumption as occurring alone and without other substances, but the bits of epidemiological evidence we have suggest that the overlap between cannabis, alcohol and tobacco is actually quite strong, in particular the overlap between alcohol and cannabis, so that when we are looking at effects we are not just looking at people who chose one substance, we are looking probably at a sub-group within the population who consume a lot of different substances. So the health effects then have to be considered (1) in the context of what might be the cumulative effect of that and (2) if, for instance somebody was wishing to modify behaviour, in what way would the other substance potentially affect their capacity. This is entirely speculative in that we do not have good longitudinal data. We do know, however, within the treatment population, 80 to 90 per cent of people attending drug clinics report cannabis consumption. We know that the reported ever cannabis consumption in the young prison population, in the reported usage, is in the 60–80 per cent range, and we know in the homeless population with substance problems, alcohol, tobacco, cannabis and other drugs overlap very strongly.

*Lord Nathan*

217. Could you help us on your assessment of the impact on public health of the decriminalisation of cannabis use in the Netherlands? I have in mind the evidence of the number of teenagers who take to cannabis and who give it up before the age of 24 or some such age? It seems to me those two questions may be related.

(*Dr Farrell*) Thank you for that fascinating question, and it is clearly a fascinating question, and it would be nice to be able to answer with high quality scientific information. I have to say that probably the one person who has written most clearly about this is Professor Peter Reuter from the University of Maryland who published an article in *Science* last year comparing US and Dutch drug policies. His basis is looking at the prevalence figures; it is wrong to actually extrapolate prevalence figures to either health or social consequences, and there are no other data on the health and social consequences. He would argue that the data available makes it difficult to reason by analogy and compare the different cultures particularly in the context where cannabis prevalence has been going up in many societies irrespective of their different policies.

*Lord Rea*

218. This is slightly outside our remit but is not one of the public health consequences in Holland that the age of the chronic heroin addict population is actually going up because there are less new recruits, and some people are suggesting that this is because of the freer availability of cannabis?

(*Dr Farrell*) It is a pretty wild extrapolation to talk about what is happening with one's heroin addiction population and what is happening with the cannabis consumption market. Reuter argues that the claim that the Dutch policy has managed to disentangle the cannabis market and the hard drug market does not stand up to statistical analysis. The factors influencing recruitment of the young population into heroin dependence and the development of problems is much more complex than simply what the policies on cannabis will be.

*Lord Soulsby of Swaffham Prior*

219. The final question is that you say there is no over-dose risk with cannabis, and yet there have been five recorded deaths involving cannabis and no other drug between 1993 and 1995. Were there other factors other than drugs involved in these deaths? If not, how do you account for this apparent discrepancy?

(*Dr Farrell*) The first thing one should learn is never to say never, because somebody will find a case! That said, of the five deaths between 1993 and 1995 in which cannabis was the only drug mentioned on the death certificate, two did actually also mention alcohol, and all the five deaths involved inhalation of stomach contents. Inhalation may occur when intoxication of alcohol or drugs suppresses the normal cough reflex in an unconscious or deeply sleeping subject. In the same period, there were 59 deaths from inhalation of stomach contents in which the only substance mentioned was alcohol, and 231 in which alcohol and other intoxicants were mentioned. These figures are based on the coroner's certificate of cause of death after inquest. The certificates do not state whether the presence of other drugs was excluded by toxicological tests, though all five had been subject to post mortem and inquest.

*Lord Porter of Luddenham*

220. This is a bit like the motor accidents, in a way, is it not? What about the other people who died? What does this "involving cannabis" mean? Five deaths involving cannabis. There were hundreds of deaths not involving cannabis, presumably.

(*Dr Farrell*) I think one of the things when one looks at coroners' reports is that one has to realise the limitations of the information involved.

221. I do not know what this means. It could mean two things. It could mean deaths in which the autopsy showed cannabis was in the blood, or it could mean the illness involved cannabis, and these are quite different. It is rather like the motor accidents: how many people died who did not have this? What is the statistical significance of the fact five people who died had taken cannabis, if that is all it means, when 5,000 had not?

---

5 May 1998]DR MICHAEL FARRELL, DR SHEILA ADAM,  
MISS JUDY SANDERSON AND DR BRIAN DAVIS[Continued

---

Lord Porter of Luddenham *contd.*]

(Dr Farrell) I think it is consistent with our appraisal of the mortality risks of cannabis, which is that it is low.

*Lord Walton of Detchant*

222. Are you making the assumption that because these individuals died from inhalation of stomach contents, they were so intoxicated by cannabis that they had not been able to prevent that happening? Is this your interpretation?

(Dr Farrell) I am reporting to you, at your request, the available information on five deaths where it would appear that inhalation of vomitus was the mechanism of death, and that five of them were positive for cannabis.

*Lord Soulsby of Swaffham Prior*

223. Would this be associated with an over-dose? The inability to clear vomit from the respiratory system?

(Dr Farrell) It could possibly be associated with an intoxication effect, where there is some central nervous system suppression.

*Lord Dixon-Smith*

224. Before we finish, I wonder what Miss Sanderson might feel about this.

(Miss Sanderson) I did not know anything about cannabis six months ago when I took the job I am

doing now. Having read the literature, I would not smoke it myself but as far as I know I am not suffering from a terminal disease, and other people's decisions have to be other people's decisions.

*Lord Rea*

225. We were thinking in particular in your role as looking after the NHS services for the physically disabled.

(Miss Sanderson) We receive distressing letters from people with multiple sclerosis who take cannabis, but we also receive distressing letters from a lot of other people with illnesses which we deal with where equally there is no solution at the moment. So this is not an exception, it just has the added frisson of the cannabis question in this particular case. We receive I suppose three or four letters every week from people with multiple sclerosis, questioning the Government's policy on cannabis, and that is not a lot in the great totality of things.

226. And they are mostly claiming to get some benefit from it, are they?

(Miss Sanderson) Not everyone, but mostly.

---



5 May 1998]

[Continued]

## Examination of Witnesses

PROFESSOR JOHN STRANG, Director, and MR JOHN WITTON, Researcher, National Addiction Centre, Institute of Psychiatry, were called in and examined.

*Chairman*

227. Professor Strang, Mr Witton, thank you very much for coming.

(*Professor Strang*) Would it help if I introduced John Witton and the nature of our joint work as a start to our evidence?

228. Yes please.

(*Professor Strang*) It goes back a few years to when I became aware myself of what I considered to be the poor quality of the cannabis debate in this country. Cannabis had not been, and still to some extent is not, a drug that has been a particular interest of mine within the addiction sphere. Obviously, for all people here there will be areas in which you specialise more than others, and in my career probably the heroin problem and the HIV problem were my bigger areas of speciality. Being involved on the edge of the cannabis debate, I was disappointed by the lack of objectivity of the debate and by what it seemed to me was a confusion between different areas of the debate, so if there were issues around therapeutic uses it seemed to me one could address those in a fairly well circumscribed way without having to deal with all aspects of the cannabis debate. On the basis of my dissatisfaction with the quality of the debate, we sought and eventually secured funding from a charity to set up a project, and John Witton is the living embodiment of the project, where we would not conduct any original research but would go through a rolling programme addressing each of seven or eight what seemed to me to be well-circumscribed areas where we could gather the evidence on those seven or eight areas and during the course of the project, on which John Witton and I are working together, we would be able to deliver our synthesis of the available data. As I am sure you will be aware, there is a huge amount of literature out there and part of the difficulty is digesting that volume of material and working out which bits are significant and which bits are noise in the system. Having secured the funding, we then sought and recruited to the post, and John Witton was appointed in the latter half of last year and began in post at the beginning of this year, and we will be working on this over the next two to three years.

*Lord Rea*

229. From your experience, what do you understand to be the most serious effects of long-term cannabis use? We have discussed the short-term effects, but it is the long-term ones we are really concerned about.

(*Professor Strang*) I perhaps need to warn you in advance—and I do not know whether it is a problem or a strength to the different bits of evidence you have received, a number of us work together and Dr Farrell who was in this chair in the previous evidence is in a different capacity a colleague of mine and all of us have been very strongly influenced by Professor Wayne Hall's recent work over the last five years or so from Sydney. So if there is a similarity to some of

our replies it is because we have been similarly influenced. In answering that question, if I may, I will pass over to my colleague, Mr Witton.

(*Mr Witton*) As Professor Strang has said, much of the findings of the research have been well-rehearsed in some of the substantial reports you have probably seen already. The report which came out from the World Health Organisation last year does tend to support the findings from Wayne Hall's summary of literature, *The Health and Psychological Consequence of Cannabis Use*, which I expect you have all seen already. If the Committee would like me to do so, I could quickly read out the summary from that report, but I assume you have seen it already.

*Lord Rea*

230. You could almost summarise the summary.

(*Mr Witton*) I have heard it as well this morning from the Department of Health, so I think we have been through it enough times already. As far as my scanning of the literature is concerned, I have not seen anything thus far which would want me to add anything to Wayne Hall's findings.

231. But are there any particular aspects you would like to bring out and emphasise which are areas of controversy and where, particularly, more work needs to be done?

(*Mr Witton*) The whole area of long-term use is very much an area where research was stalled in the early 1970s and we do need a great deal more work in this particular area. As Dr Farrell mentioned earlier, there have been some useful bits of work on dependence on cannabis in Australia, but it is very early days to test the significance of those findings. Certainly I would alert the Committee to the area of cannabis dependence as one which needs to be followed up quite strongly. Certainly the question of some element of cognitive impairment due to cannabis use is an area I shall be looking at quite closely. As you have drawn attention to as well, this brings into the area for question educational performance, driving ability and work performance, so those are the areas I will be looking out for.

232. When you talk about those areas, are you talking about the residual effects after someone has taken it for a long time or the continuing dose effect?

(*Mr Witton*) It will be the latter, the continuing dose effect.

233. What about the residual effects after someone has taken cannabis for a number of years?

(*Mr Witton*) That is going to be something where I am not sure the research is going to be so helpful just at the moment, but I think I will have to go back to the plethora of research undertaken in North America in the late 1960s, early 1970s, and see what that research shows up.



5 May 1998]

PROFESSOR JOHN STRANG AND MR JOHN WITTON

[Continued]

*Lord Porter of Luddenham*

234. I wonder whether, as psychiatrists, you can say anything about the psychiatric effects of the synthetics, Nabilone and so on, which you have heard us talking about, compared with natural cannabis?

(*Professor Strang*) Just to clarify, we come from different backgrounds. I come from a medical background and I am a psychiatrist, and John Witton's background is as an academic and a non-clinical background. So we give slightly different perspectives on this. I have very little knowledge about the impact of the synthetic cannabis derivatives and their psychiatric effects, and would know no more than you heard this morning about the evidence that psycho-active effects are a feature of these drugs when they are used for their anti-emetic effects. They have been used in a number of different clinical trial applications. But I think I am just repeating hearsay, I am not contributing any valuable, original evidence.

235. Have there been tests outside the ordinary clinical trials of the psychiatric effects of Nabilone and synthetics?

(*Professor Strang*) I am afraid I am unable to help you either one way or the other.

236. I thought that would be the answer, but I thought if you had some evidence we would like to have it.

(*Mr Witton*) I can certainly advise the Committee at a later stage of the evidence and research there. My recollection is that there is, but I cannot bring the research to mind.

237. We would like to have that.

(*Mr Witton*) I would be quite happy to research that.<sup>1</sup>

*Lord Walton of Detchant*

238. About 30 years ago there was a paper published in *The Lancet*, I think from Bristol, suggesting that in long-term heavy cannabis use there was evidence of a subtle dementia which was associated with enlargement of the cerebral ventricles and a degree of cortical atrophy. Very properly that paper was criticised as not being as scientifically rigorous as one might have wished. As you say, since that time evidence has emerged that long-term use may be associated with cognitive decline and Professor Griffith-Edwards, when he talked to us, said that Dr Nadia Solowij had done some work which suggested these subtle cognitive impairments may not revert to normal when people stopped taking the drug. Can you comment on this?

(*Professor Strang*) I am pleased to say that both of us know of the paper from Bristol which you mentioned, and your comments about it are correct; it received a huge amount of media attention at the time. The difficulty, which you will be only too aware is before you, is working out which bits of evidence you assign what weighting to. The work which you

mentioned, to which Professor Griffith-Edwards drew your attention, I suspect you know no more about than I do. I am aware of it, I have spoken with Griffith-Edwards about it but just in conversation, and I believe you have seen a précis of the work which means you are now ahead of me in terms of your knowledge of that particular paper. I hope in the months ahead Mr Witton and I will become much more familiar with it and will try to work out how it fits within the picture of the large volume of work, but we cannot help at this stage. If I might comment, I do think one of the particular difficulties that you must be encountering is the amount of hearsay which is presented to you, where you merely have one person's opinion of someone else's précis of a newspaper report they saw, a bit of work not yet published. I do think in this area it is vital to go back to the basic principles of looking at the quality of evidence presented, and looking at the nature of the adequacy of the peer review of the data presented, the very same criteria that we would apply to any other field, despite the general public's wish for quick answers.

239. How strong do you think the evidence is to confirm the view widely expressed that cannabis use may exacerbate the symptoms of schizophrenia? Secondly, there are many psychiatrists who believe that cannabis alone, apparently not in susceptible individuals, may promote or may produce delusions and hallucinations, a kind of cannabis-induced psychosis which may be misdiagnosed as schizophrenia. What is your view about these two possibilities?

(*Professor Strang*) If I might put a clinical hat on for this answer. I have no doubt that both those statements are correct, that cannabis can exacerbate, aggravate or precipitate a recurrence in the course of illnesses such as schizophrenia and probably for other conditions such as manic depressive illness, and it then becomes one of the insults which one can identify as precipitating a relapse. In that regard, it then stands alongside other adverse life events which we also know precipitate relapses or recurrences in an already established chronic mental illness. I also have no doubt, and have seen instances of, an acute psychotic episode, a transient psychotic episode, might be likened to being similar to the toxic psychoses you see with all manner of substances. I would agree entirely with the point that I took to lay behind your question, that there is a great danger in confusing that time-limited drug-induced psychosis with a first instance of a chronic relapsing condition, and hence diagnostically it is crucial to know whether the first episode of transient psychosis in a young adult was or was not accompanied by cannabis in the system at the time. If I had been paid a small amount of money for each time I am asked to comment in retrospect on whether someone's psychotic episode of three months' ago was or was not cannabis-induced or schizophrenia, I would be a rich man by now. Clinically, it would be so simple if only clinicians understood they should routinely collect the urine specimen. Picking up a point I heard in the earlier evidence, if they get cannabis positive in the urine it does not establish a causal relationship, but a negative for cannabis at the time of a transient psychotic episode helps you with your positive diagnosis of schizophrenia.

<sup>1</sup> Subsequent note from witness: As promised I conducted a literature search for material on tests outside the ordinary clinical trials of the psychiatric effects of Nabilone and other synthetics. The search was unsuccessful and I was unable to uncover any research on this topic.



5 May 1998]

PROFESSOR JOHN STRANG AND MR JOHN WITTON

[Continued]

*Chairman*

240. Would it be right to say that the transient psychosis passes off, and similarly if it makes the schizophrenia worse does that also not disappear? Or does it last?

(*Professor Strang*) The evidence which I can recall, as I am sitting here—and if I remember other evidence perhaps I might write in to correct it at a later stage—has been of it precipitating a relapse. If I remember correctly, I have not seen evidence that the nature of that relapse is then itself different, but the persistence of cannabis use is associated with poor prognosis. Whilst I have been speaking in a clinical capacity, what I would typically do when I was unsure of the data, is go along to John Witton's office to ask him what the research evidence actually said, and if you will allow me to do so I will deflect the question on to John Witton in case there are other areas to mention.

(*Mr Witton*) I think Professor Strang has answered the question about schizophrenia quite fully from his own background. If someone was to ask me about literature and research, as usual I would be deferring to Wayne Hall and his work. I do not know if the Committee has seen his summary of the literature on cannabis psychosis which he published last year but he has done a rigorous review of the literature. He does not come to any conclusions but points up the possibilities of both organic psychosis and functional psychosis being associated with cannabis use, but he does not go into detail as to the likelihood of this happening. But, yes, both possibilities do exist.

*Lord Rea*

241. Could I ask how this psychosis-inducing property compares to the effect of alcohol in doing the same?

(*Professor Strang*) I think I am not able to give you a very good answer on that.

242. Put on your clinician's hat, which means you have to act on what evidence is in the back of your head!

(*Professor Strang*) Yes. My reason for caution is that I am not wanting to reach a conclusion which I do not feel I can then defend. Both drugs are associated with significant acute psychiatric complications in that immediate period. I would presume that if I had either now or at certain future date of our understanding a better awareness I would know not only how frequently it occurred, if it occurred, in cannabis users but which component of cannabis or which components were responsible for that. I presume there will be one or a cluster of the components which are the reason for that acute episode and the long-term effects. I would also obviously wish to have a much better understanding of the dose relationship to that effect. I do know from clinical experience that there are some individuals who have presented with acute psychiatric states from what their peers regarded as perfectly normal doses of cannabis, but whether that is just that they are more efficient at absorbing it or whether they are constitutionally more sensitive to it, or whether it is a different mechanism, I do not know and I am not aware of evidence from others which will help me to know that difference.

243. You are suggesting that cannabis in normal doses might do it, whereas alcohol in "normal doses" usually does not?

(*Professor Strang*) Well, I can see the logic of the distinction you are making but I just do not know how firmly I would stand on the ground you suggest I stand on. I am sorry to be slightly elusive.

*Chairman*

244. What I was trying to get at is how seriously you regard these two complications or side effects in the potential use of cannabis?

(*Professor Strang*) The number of occasions on which somebody seeks hospital admission or hospital help with an acute psychiatric illness which seems to be related to cannabis is a very small number of instances compared with the number of instances of cannabis use. Obviously for those individuals it can be extremely disturbing, and I know of a small number of patients I have individually treated for whom it has triggered a series of panic attacks which then assumed a life of their own, and that has also been written up in the literature. Also in terms of the management of the long-term mentally ill, I know, not so much from my own work but from colleagues handling large caseloads of the generally mentally ill, it is a major problem that they have to grapple with; the pattern of cannabis use which was seen by some of their patients as part of their normal pattern of behaviour, which leaves them more at risk of relapse and the difficulties of addressing that. I cannot remember whether it was in the written papers from Wayne Hall or in the presentation he gave at the National Addiction Centre when he visited us last year, but he commented on the extreme rarity with which clinicians had ever addressed cannabis use in the regular cannabis users. In discussions, he and I commented on the fact that it was as if the pendulum had swung from perhaps 30 years ago, when it would automatically have been seen as a major issue that clinicians addressed, to now, an area where clinicians did not give advice on cannabis with regard to other areas, like mental health. If I remember correctly he either said that none of these regular cannabis users, or only a very small number—I cannot remember which it was—had ever been advised to alter their cannabis use by clinicians who knew of their cannabis use.

*Lord Winston*

245. Can we do a bit better in the field of addiction? Would you like to give us your impressions of how likely regular users of cannabis are to become addicted?

(*Professor Strang*) I think we can do a little better, and again I would refer to other people's work.

(*Mr Witton*) Which is Wayne Hall again. The figure of 40 per cent was mentioned by Mike Farrell from some of Wayne Hall's work in Sydney with long-term cannabis users. Of course it depends what definition of dependence we are using. Wayne Hall and his colleagues were clear they were not thinking in terms of the classic dependence syndrome, when you have chronic physical withdrawal symptoms, they are talking about inability to give up for



5 May 1998]

PROFESSOR JOHN STRANG AND MR JOHN WITTON

[Continued]

Lord Winston *contd.*]

psychological reasons. It is also quite clear that it is difficult to extrapolate too broadly from the findings of this work because they are long-term users and not your normal recreational user. The figure that Wayne Hall and his colleagues came up with was that of the 200 people they interviewed, about 40 per cent of them they considered to have severe dependence problems according to the scale of measurement they used, the American Psychiatric Association's Diagnostic and Statistical Manual III.

246. Are you talking here of people who have perhaps used the drug casually on one or two occasions, or people who have used the drug regularly and then have become addicted?

(Mr Witton) It is the latter, the people who have used regularly, it is not the recreational user. That is why the research has to be handled quite carefully.

247. And the crunch question, of course, is what about other addictive agents? We have heard about alcohol, for example, but there are those addicted to smoking and more serious addictive agents. Where would you put it on the scale of addictive agents?

(Professor Strang) Just before I pick that up, could I say that I think the distinction you have made is hugely important in attempting to interpret the data. In reporting on this work, we are talking about 40 per cent of a group recruited on the basis of being regular users were then found to report features that one could recognise as cannabis-dependence syndrome. The other way round, looking at if you had a starter's gun of 100 people who began their first use of cannabis today, what proportion would subsequently develop problems of dependence on that cannabis, if we are allowed quite a wide margin of error I think one would see it as somewhere between 5 and 15 per cent. It is a small but not insignificant number, especially if that behaviour then becomes fairly widespread within society. But that is a ballpark figure for the wider question. If I might move on to the rider question you just asked about how does it compare with other drugs. You will be aware that this is a political minefield, as demonstrated by the fact that in Wayne Hall's document, it is considered. I am sorry to be ducking so many questions or referring on so many questions to the way in which he has addressed it, but I am not only impressed by the comprehensiveness of his work but also by the subtlety with which he has tried to address the political and wider social policy issues. In his monograph documents he does address this issue of how one sees it as a drug within society, and in what ways is that similar or different from how one views alcohol and tobacco, whereas the WHO document, to which he contributed significantly, I think I am correct, quite specifically did not have that comparison in it. There are obvious useful similarities but I find myself not very helped by those comparisons, and with a policy hat on I am more interested in whether a small incremental change in the present *status quo* leads to increased or decreased harm within society, whether we might have a good solution or an unholy mess with particular other drugs like alcohol and tobacco. I am always puzzled when alcohol and tobacco are held up as great examples of how well it can be handled when you look at the enormous harm they bring to society.

248. But it does give us a little idea as to how serious the addiction is when it comes to kicking the habit, and therefore it is a relevant question.

(Professor Strang) That is the way in which it is useful. It is addressed in his book and it becomes usefully comparable, in terms of understanding that, from a starting cohort, a small number will develop dependence and another group will develop harms that relate to acute intoxication effects. Those same principles are usefully borrowed across from the alcohol field with which we are so much more familiar. It then leaves unanswered the question about whether the other scientific laws which we understand govern alcohol consumption carry across. We now know we can alter the levels of alcohol consumption, the levels of harm within society, the levels of road traffic accidents, by a variety of means. Do those same laws apply to the control of other drugs such as cannabis? One's hunch is that they do, but I am talking hunches now, not concrete evidence, I am afraid.

Lord Walton of Detchant

249. An afterthought related to my previous question: accepting the problems about defining a standard preparation of cannabis and a standard route of administration, many of those with multiple sclerosis claiming benefit on their spasticity say they take only a very small dose of cannabis with beneficial effect and try to keep the psycho-active consequences at a minimum. Are you aware whether any of these serious psychiatric complications, such as acute psychosis, ever occur at a very low dose level, or does it require heavy dosage?

(Professor Strang) I certainly know of individual patients who have had quite acute psychiatric problems from very low doses. However, if I were in a position of trying to take that on board in considering a new drug treatment for the nausea of chemotherapy or multiple sclerosis or glaucoma, or any one of a number of areas of claimed possible therapeutic benefit, I would put that in my risk-benefit equation. I would just say that there may be a small number of patients who suffer this adverse consequence. If we have the opportunity to raise areas that we thought you might want to ask us about but had not, therapeutic uses was one I had listed. I do feel that the debate gets distracted by the wider issue about personal freedoms and legalisation and decriminalisation, and I would expect to see cannabis, which is a sort of rich, dirty product with 400 chemicals and 60-something different cannabinoids, being applied to the same rigorous exploration and extraction of the active ingredients, as one would expect to see for any other medicine which appears on the shelf. I would be very disappointed to see such work obstructed and I would also be worried if it was given some easy track so it was not subjected to the same rigorous studies as other products. Hence moving into the realms of, "Let's pick up a batch of leaves from wherever and try and develop a standardised batch of leaves which you then roll up, burn and inhale", one is creating almost insuperable obstacles. I would expect greater progress to be made by trying to pick off what one



5 May 1998]

PROFESSOR JOHN STRANG AND MR JOHN WITTON

[Continued

Lord Walton of Detchant *contd.*]

expects to be the psycho-active ingredients, and, if you want, a larger short-list because you are not sure which it is, but to approach it from that point of view. I think in the longer-term it would be more likely to be productive.

*Chairman*

250. Are there any other comments you would like to add?

(*Professor Strang*) Just a few rounding-up points to do with the therapeutic uses, because it seems to me such an important question at the present time. I must apologise if I am saying points which are obvious, but they are to some extent addressing the general public's debate rather than your own debate. I am always suspicious when people talk about natural products, as if somehow natural products have some intrinsic greater safety or advantage. I would find myself wanting to know what it was within the soup which was being considered which was the active ingredient, and without doing so I do not see how one could ever standardise the product. It is possible, and I think I heard Dr Sheila Adam saying in the earlier evidence, there may be

interesting interactions between several of those products, but again I see this as a proper area of development of medicines and it is not a matter of just following it through with pretty messy products.

251. I spent a large part of my life doing biological standardisation, and it is possible to standardise biologically mixtures from natural products, and we did it with digitalis.

(*Professor Strang*) Indeed, and I would have thought that was the sort of approach one would expect to see developed, rather than somehow thinking you would be able to develop a sort of House of Lords standardised cannabis formulation. The raw product varies so enormously that, if you were to select one of the raw products and managed to invest a huge amount of time and energy in testing that raw product and found it was not very valuable, you would not have ruled out the fact that one of the other raw products might have been the one which was more effective. So I would presume to take that huge body of scientific work and roll it out into this area. There are no other points to add.

*Chairman*] Thank you very much indeed, we are most grateful.

---

TUESDAY 12 MAY 1998

---

Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Porter of Luddenham, L.

Rea, L.  
Soulsby of Swaffham Prior, L.  
(in the Chair)

---

**Memorandum by Dr Roger Pertwee, University of Aberdeen**

## CONTENTS

1. The Endogenous Cannabinoid System
2. Therapeutic Potential of Cannabinoids
3. References

## 1. THE ENDOGENOUS CANNABINOID SYSTEM (Pertwee, 1997a)

1.1 The plant *Cannabis sativa* is the unique source of a set of more than 60 oxygen-containing aromatic hydrocarbon compounds called cannabinoids. Among these is  $\Delta^9$ -tetrahydrocannabinol to which most of the known pharmacological properties of cannabis can be attributed. It is now known that the main effects of  $\Delta^9$ -tetrahydrocannabinol are mediated by specific cannabinoid receptors, two types of which have so far been identified. These are CB<sub>1</sub> receptors, discovered in 1990, and CB<sub>2</sub> receptors, discovered in 1993. Both these receptor types are coupled to their effector systems through G<sub>i/o</sub> proteins. CB<sub>1</sub> receptors are present in the central nervous system as well as in certain neuronal and nonneuronal peripheral tissues whereas CB<sub>2</sub> receptors are found mainly in cells of the immune system. The possibility that mammalian tissues express additional cannabinoid receptor types of physiological significance cannot be excluded. Indeed, preliminary pharmacological evidence that supports this possibility already exists. Another important recent discovery has been that mammalian tissues produce compounds that can activate cannabinoid receptors, the most important being arachidonylethanolamide (anandamide) and 2-arachidonoyl glycerol. These "endogenous cannabinoids" and their receptors constitute the "endogenous cannabinoid system". Further details about the pharmacology of cannabinoids and their receptors can be found in a recent review (Pertwee, 1997a).

1.2 The distribution pattern of CB<sub>1</sub> receptors within the central nervous system is heterogeneous, unlike that for any other receptor type and consistent with the known ability of cannabinoid receptor agonists to impair cognition and memory, to alter motor function and movement and to relieve pain (Pertwee, 1997a). The highest concentrations of cannabinoid binding sites in the brain are in the basal ganglia (substantia nigra pars reticulata, the entopeduncular nucleus, the globus pallidus and the lateral caudate-putamen). Other areas of the brain quite rich in cannabinoid binding sites include the hippocampus, cerebral cortex, intrabulbar anterior commissure, nucleus accumbens, septum, olfactory bulb and molecular layer of the cerebellum. Among areas of the brain less densely populated with cannabinoid binding sites are the central gray substance, the area postrema, the caudal nucleus of the solitary tract, the amygdala, thalamus, habenula, preoptic area and hypothalamus, and much of the brain stem. Regions of the spinal cord that are richest in cannabinoid binding sites are lamina X and the substantia gelatinosa.

1.3 Some CB<sub>1</sub> receptors occur at central and peripheral nerve terminals and these are known to reduce transmitter release when activated. Hence one of the physiological roles of these receptors is probably to modulate the release of central and peripheral neurotransmitters in certain pathways. The part played by cannabinoid receptors in the production of some of the effects of cannabis in the whole organism remains to be established. Among the effects of cannabinoids already known from animal experiments to be mediated by CB<sub>1</sub> receptors are antinociception (analgesia) and changes in memory, motor function (hypokinesia and catalepsy), thermoregulation (hypothermia), memory, gut motility (inhibition) and transmitter release (inhibition).

1.4 Little is yet known about the physiological role(s) of the more recently discovered CB<sub>2</sub> receptor although it seems likely that this will prove to involve modulation of immune function in health and/or disease. It is vital that further research is funded to elucidate the physiological and pathophysiological role(s) of this receptor type as this may well reveal important new clinical applications for cannabinoid receptor agonists or antagonists. Additional research is also urgently needed to establish the mechanisms underlying effects of cannabinoids of known or potential therapeutic value (section 2): it is noteworthy that almost nothing is known even about the mechanisms underlying the two effects of cannabinoids that it already is



12 May 1998]

[Continued

permissible to exploit for therapeutic purposes in the UK or USA: antiemesis and appetite stimulation (para 2.1).

## 2. THERAPEUTIC POTENTIAL OF CANNABINOIDS (Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b).

2.1 As well as having physiological importance, the discovery of the endogenous cannabinoid system has significant pharmacological and therapeutic implications. Indeed, drugs that selectively activate CB<sub>1</sub> or CB<sub>2</sub> receptors (agonists) or selectively block one or other of these receptor types (antagonists) have already been developed. Moreover, one cannabinoid receptor agonist, nabilone (Cesamet ®), is currently used clinically in the UK. This drug, a synthetic analogue of  $\Delta^9$ -tetrahydrocannabinol, is licensed for use as a suppressant of nausea and vomiting provoked by anticancer drugs. In the USA,  $\Delta^9$ -tetrahydrocannabinol itself is prescribed for this purpose and also to boost the appetite of AIDS patients and so reduce or reverse loss of body weight. The formulation used,  $\Delta^9$ -tetrahydrocannabinol in sesame oil, is called dronabinol (Marinol ®). The introduction into the clinic of  $\Delta^9$ -tetrahydrocannabinol and nabilone as antiemetics preceded the development of ondansetron and no clinical studies directed at comparing the efficacy of this excellent new anti-emetic with that of  $\Delta^9$ -tetrahydrocannabinol or nabilone have yet been carried out. The licensed use of cannabinoids as antiemetics/appetite stimulants will not be discussed further in this document as it is presumably not a contentious issue.

2.2 As detailed elsewhere (Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b), additional therapeutic uses of cannabinoid receptor agonists may include the suppression of some symptoms associated with multiple sclerosis, with spinal injury and with certain other movement disorders (eg muscle spasticity/spasm) and the management of glaucoma, bronchial asthma, pain and inflammatory disorders. The CB<sub>1</sub> receptor antagonist, SR141716A, may also have therapeutic uses, for example in reducing memory deficits associated with ageing or neurological diseases (Pertwee, 1997a). The evidence supporting the use of cannabinoids for multiple sclerosis and spinal injury, for pain, for primary open-angle glaucoma and for bronchial asthma is particularly promising and is therefore discussed further in paragraphs 2.3, 2.4, 2.5 and 2.6.

2.3 The evidence that cannabinoids would be effective in relieving spasticity, tremor and pain caused by multiple sclerosis or spinal injury is based on preclinical, anecdotal and clinical data (see Pertwee, 1997b for references). More specifically, animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes, produce marked behavioural changes in motor function, for example hypokinesia and catalepsy, and have significant efficacy in standard tests of antinociception (analgesia) (see also para 2.4). The effects on motor function are no doubt mediated at least in part by the large populations of cannabinoid CB<sub>1</sub> receptors that are present in the basal ganglia of the brain (see para 1.2). Whether cannabinoids produce their putative antispasticity effect by acting at these brain sites remains to be established. There is also good evidence that cannabinoid-induced antinociception is centrally mediated, in this case at sites within both brain and spinal cord (see also para 2.4). In addition, experiments with rats and guinea-pigs have shown that tetrahydrocannabinol can delay the onset and reduce the intensity of the clinical signs of experimental autoimmune encephalomyelitis, a putative animal model of multiple sclerosis. Also relevant is a report that the synthetic cannabinoid receptor agonist, WIN55212-2, can decrease the severity of dystonia in mutant Syrian hamsters with primary generalized dystonia. As to the anecdotal data, these are to be found in numerous newspaper reports and also in responses to a recent questionnaire we distributed to multiple sclerosis patients who self-medicate with cannabis (Consroe et al, 1997). Of the 112 subjects in this survey who were experiencing the following symptoms, the percentage reporting improvement after taking cannabis was 96.5 per cent for spasticity at sleep onset, 95.1 per cent for pain in muscles, 93.2 per cent for spasticity when waking at night, 92.3 per cent for pain in the legs at night, 90.7 per cent for tremor of arms/head and 90.6 per cent for depression. The numbers of subjects reporting these symptoms were respectively 86, 61, 59, 52, 43 and 74. Because this survey targeted multiple sclerosis patients who self-medicate with cannabis, the data it generated cannot be used to predict the proportion of all multiple sclerosis patients who might benefit from cannabis. The clinical data supporting the use of cannabinoids for multiple sclerosis or spinal injury come from seven clinical trials, albeit with rather small numbers of patients. These indicate that cannabis,  $\Delta^9$ -tetrahydrocannabinol or nabilone can reduce the intensity of at least some signs and symptoms of multiple sclerosis or spinal injury, particularly spasticity, pain, tremor and nocturia. Additional clinical evidence that cannabinoids are analgesic is described in para 2.4. Better designed, more extensive clinical trials are now needed that will test the efficacy of cannabis or individual cannabinoids against signs and symptoms of multiple sclerosis and spinal injury more conclusively.

2.4. With regard to pain relief by cannabinoids, there are some reports from human studies that  $\Delta^9$ -tetrahydrocannabinol or cannabis do not have an analgesic effect (no detectable effect on experimental or post-operative pain perception; Hill et al, 1974a; Karniol et al, 1975; Raft et al, 1977; Regelson et al, 1976) and others that cannabis can increase sensitivity to tactile stimulation or experimental pain (Hill et al, 1974a, b; Clark et al, 1981). On the other hand, several anecdotal accounts of the ability of cannabis to relieve chronic pain are to be found in the book by Grinspoon & Bakalar (1993). To these may be added results from a survey of 10 spinal cord injured patients in which cannabis-induced reductions in pain (and spasticity) were claimed



*12 May 1998]**[Continued]*

(Dunn & Davis, 1974) and results from a case study with one amputee indicating orally administered  $\Delta^9$ -tetrahydrocannabinol (dronabinol/marinol) to be markedly more effective than conventional drug treatments in reducing the incidence of phantom limb pain episodes (Finnegan-Ling & Musty, 1994). The ability of cannabinoids to relieve chronic pain has also been investigated in placebo controlled clinical trials using either  $\Delta^9$ -tetrahydrocannabinol (administered orally or intravenously) or the synthetic cannabinoids, levonantradol (injected intramuscularly) or nabilone (Noyes et al, 1975a; 1975b; Jain et al, 1981; Hollister, 1986; Pertwee, 1997a). Relatively few such studies have been carried out. Even so, the clinical data that have been obtained indicate that cannabinoids are capable of bringing about relief from continuous moderate pain arising from surgery or cancer or associated with multiple sclerosis or spinal cord injury. The idea that cannabis,  $\Delta^9$ -tetrahydrocannabinol and its synthetic analogues are effective for pain relief is entirely consistent with present knowledge about the pharmacology of cannabinoids. Thus cannabinoids show analgesic activity in animals as measured in standard nociceptive tests (eg rat paw formalin test and mouse tail flick test; Tsou et al, 1996; Martin et al, 1995) as well as in a model of neuropathic pain (chronic unilateral constriction injury to sciatic nerve; Herzberg et al, 1997). The antinociceptive effects of cannabinoids seem to be cannabinoid receptor mediated as they can be readily blocked by the CB<sub>1</sub> receptor antagonist, SR141716A (Rinaldi-Carmona et al, 1994; Compton et al, 1996; Lichtman & Martin, 1997; Herzberg et al, 1997). It is also known that cannabinoid CB<sub>1</sub> receptors are present in areas of the central nervous system that control pain perception. These include the brain stem and the substantia gelatinosa of the spinal cord (Pertwee, 1997a) and animal experiments have shown that cannabinoids produce signs of analgesia when they are injected directly into these sites (Lichtman & Martin, 1991; Martin et al, 1993; Lichtman et al, 1996). In this respect cannabinoids resemble opioid analgesics (which also act centrally) rather than non-steroidal antiinflammatory drugs that act outside the central nervous system, at the sites of injury. It is noteworthy that there is evidence from animal experiments that cannabinoids enhance the ability of opioids to relieve pain through delta and kappa opioid receptors in the spinal cord (Pugh et al, 1996). Moreover, in a recent case study of a patient suffering from chronic pain associated with familial Mediterranean fever, oral administration of a cannabis extract that did not itself induce detectable analgesia was found to considerably reduce the patient's requirement for morphine-induced analgesia (Holdcroft et al, 1997). Whether these findings mean that it would be of therapeutic advantage to administer a cannabinoid and an opioid in combination will depend largely on the extent to which the unwanted effects of cannabinoid and opioid drugs are also augmented after combined administration. This possibility is worth exploring further as attempts to develop non-psychoactive cannabinoid analgesics have so far proved unsuccessful. (The concept of administering an opioid together with another drug for pain relief is not new: there are several licensed analgesic preparations that contain an opioid together with a non-steroidal antiinflammatory drug.) Finally, the evidence that cannabinoids may be effective against neuropathic pain (eg phantom limb pain) is particularly worthy of note as this type of pain is currently not well managed in the clinic.

2.5 Raised intraocular pressure (glaucoma), if not checked, will produce irreversible damage to the optic nerve that will eventually lead to blindness. The most common form of this disorder is primary open-angle glaucoma, also known as chronic simple glaucoma. This is characterised by a gradual loss of both visual acuity and peripheral vision, by a blurring of vision and by the appearance of coloured haloes around bright objects. There is good evidence from experiments with animals, healthy human subjects and patients with primary open-angle glaucoma that cannabinoids can lower intra-ocular pressure (Green, 1998). The site and mode of action of cannabinoids for depression of intra-ocular pressure remain to be established as does the question of the optimal route of cannabinoid administration for glaucoma. Cannabinoids can reduce intra-ocular pressure when applied directly to the eye. However, one practical limitation when this route is used is the lack of a suitable drug vehicle. (Vehicles that have been used in experiments induce copious tear production in human subjects) (Green, 1998). Another potential problem is cannabinoid tolerance as the need for intra-ocular pressure to be kept within safe limits at all times dictates that glaucoma patients be continuously exposed to effective concentrations of their treatment drug.

2.6 Bronchial asthma is often characterised by early and late phase responses. In the early phase response, there is a narrowing of the small tubules in the lungs called bronchioles. This bronchospasm, which produces a marked increase in airflow resistance, may be caused by allergens such as pollen or house dust or by other kinds of stimuli, for example cold air, infections of the respiratory tract or emotional stress. In the late phase response, there is an acute bronchial inflammatory reaction leading to the production of mucus. Cannabinoids show promise for the treatment of the early phase response of asthma. Thus they can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatments of asthma (Hollister, 1986; British Medical Association, 1997). Both cannabis and individual cannabinoids are active when taken orally or when inhaled, either in smoke or in an aerosol produced by a nebulizer or Ventolin inhaler (Williams et al, 1976; Tashkin et al, 1977; Hollister, 1986; British Medical Association, 1997). It is noteworthy that in one study (Tashkin et al, 1997),  $\Delta^9$ -tetrahydrocannabinol administered as an aerosol induced bronchoconstriction, coughing and chest discomfort in two out of five asthmatic subjects. The mechanisms underlying the bronchodilator effect of cannabinoids remain to be established. However, only cannabinoids with psychotropic properties have so far been found to produce bronchodilation (Hollister, 1986), indicating that the effect may be cannabinoid



*12 May 1998]**[Continued*

receptor-mediated. One important priority for any further studies is the development of an improved cannabinoid formulation for administration as an aerosol.

2.7 Centrally active CB<sub>1</sub> receptor agonists have the disadvantage of maximising the incidence of adverse effects by producing indiscriminate activation of all CB<sub>1</sub> receptors. One solution could be to develop drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endogenous cannabinoids so as to increase their concentrations at cannabinoid receptors. This strategy relies on the likelihood that such drugs will not affect all parts of the endogenous cannabinoid system at one time but rather produce effects only at sites where there is on-going production of endogenous cannabinoids. Drugs that inhibit one or other of the processes responsible for the removal of endogenous cannabinoids from the extracellular space already exist (Pertwee, 1998a). This and other possible strategies for improving the benefit to risk ratio of cannabinoids are detailed elsewhere (Pertwee 1996, 1998,a,b).

2.8 There is a need for better cannabinoid formulations and modes of administration (Pertwee, 1997b; see also para 2.5 and 2.6). Thus when taken orally,  $\Delta^9$ -tetrahydrocannabinol seems to undergo somewhat variable absorption from the gastro-intestinal tract and to have a rather narrow "therapeutic window" (dose range in which it is effective without producing significant unwanted effects) (Pertwee, 1997b). For example, in a clinical study with two multiple sclerosis patients,  $\Delta^9$ -tetrahydrocannabinol was effective in one of the patients at an oral dose of 5 mg whilst in the second patient it was effective only when the dose was raised to 15 mg (both 5 mg and 10 mg  $\Delta^9$ -tetrahydrocannabinol were ineffective in this patient). In another clinical study in which eight multiple sclerosis patients were given  $\Delta^9$ -tetrahydrocannabinol or placebo by mouth, both 2.5 and 5 mg  $\Delta^9$ -tetrahydrocannabinol were ineffective in relieving spasticity, 7.5 mg was effective and 10 mg was intolerable to some of the patients (narrow "therapeutic window"). The existence of a large inter-patient variation in the oral dose level of  $\Delta^9$ -tetrahydrocannabinol that is effective combined with a very narrow "therapeutic window" for oral  $\Delta^9$ -tetrahydrocannabinol makes it difficult to predict an oral dose of this drug that will be both effective and tolerable to a patient.

2.9 Like all other drugs, cannabis and cannabinoids can give rise to unwanted effects. However, the known adverse effects of cannabinoids seem to be no worse than those of some accepted therapeutic agents. In one clinical trial with 34 cancer patients (see Pertwee, 1997b), the most commonly reported unwanted symptoms produced by  $\Delta^9$ -tetrahydrocannabinol were dizziness, sedation and dry mouth (more than 75 per cent of subjects), blurred vision (65 per cent of subjects), mental clouding (53 per cent of subjects) and ataxia, numbness, disorientation, disconnected thought, slurred speech, muscle twitching and impaired memory (27 to 44 per cent of subjects). In addition, cannabis may sometimes induce transient confusion, panic attacks, depersonalization, paranoid delusions and/or hallucinations (Paton & Pertwee, 1973; Paton et al, 1973; Chopra & Smith, 1974; Tennant & Groesbeck, 1977; Chaudry et al, 1991). Cannabis has also been reported to produce a subtle impairment of postural control (see Pertwee, 1997b).

2.10 Some individuals may be more at risk from the adverse effects of cannabinoids than others (Hollister, 1986; Pertwee, 1997b). For example, cannabis may aggravate existing psychoses and can elevate heart rate. Consequently it would be unwise to give psychotropic cannabinoids to patients with schizophrenia (overt or latent), coronary arteriosclerosis or congestive heart failure. The clinical significance of the ability of cannabinoids to retard foetal development, to induce foetal resorption in animals or to suppress immune function remains to be established.

2.11 Because of the tars and gases produced during the combustion process, smoked cannabis is toxic to airway tissue and probably also carcinogenic (Hollister, 1986; British Medical Association, 1997; Roth et al, 1998). However cannabis is also active orally. For example tincture of cannabis (a solvent extract of cannabis that it was permissible to prescribe in the UK until 1971), was taken by mouth. Also, some individuals who self-medicate with cannabis, claim to do so by ingesting cannabis leaves or cannabis resin, for example in cakes or fudge or as a drink (cannabis "tea").

2.12 Tolerance to many of the pharmacological effects of cannabinoids can readily be induced in animals and man and this tolerance appears to be mainly pharmacodynamic in nature. Present knowledge about cannabinoid tolerance in man comes largely from work carried out before 1981. There have been a number of laboratory studies (Abood & Martin, 1992; Pertwee, 1991). These were performed with experienced cannabis users and fall essentially into two categories. The first consists of experiments which have examined the relationship between subject's self-reported rates of cannabis consumption (outside the laboratory) and responsiveness to cannabis/cannabinoids measured in the laboratory. The second category is made up of studies that have investigated the extent to which tolerance can be induced by tetrahydrocannabinol or cannabis when these are repeatedly administered in a controlled environment. The results from both types of study provide good evidence that tolerance can develop in man to many of the effects of cannabis and tetrahydrocannabinol. These include effects on mood, memory, EEG, sleep, heart rate, blood pressure, intraocular pressure, body temperature, salivary flow and performance in psychomotor tasks. Tolerance may also develop to the antiemetic effect of  $\Delta^9$ -tetrahydrocannabinol. Human experiments, like those with animals, have yielded data which suggest that tolerance to cannabinoids can develop rapidly and that the rate of onset of cannabinoid tolerance is affected by the pretreatment dose and by the frequency with which this is administered. Most tolerance studies with human subjects have been conducted without double-blind or placebo treatments. This is an important limitation since there is evidence that certain responses to cannabis

12 May 1998]

[Continued

can be markedly influenced by the "expectation" of subjects. An additional interpretational difficulty associated with many of those studies in which the development of tolerance has been followed in the laboratory arises from the practice of allowing dose levels and frequency of administration to be decided by the subjects themselves. It is noteworthy, therefore, that the production of tolerance by oral  $\Delta^9$ -tetrahydrocannabinol has been clearly demonstrated in one set of experiments with 12 human subjects in which drug administrations were made double-blind and in which placebo treatments and predetermined drug regimens were used (Jones & Benowitz 1976). It is also noteworthy, however, that rather high oral doses of  $\Delta^9$ -tetrahydrocannabinol were used in this study (initially 70 mg per 24 hours in divided doses of 10 mg every 4 hours plus 20 mg at bedtime and later, 210 mg  $\Delta^9$ -tetrahydrocannabinol per 24 hours). The important question of whether cannabinoid tolerance to sought-after effects develops significantly in man when "clinically relevant" dose regimens are used still needs to be addressed.

2.13 Withdrawal of cannabis or of psychotropic cannabinoid administration can precipitate abstinence signs in man (Abood & Martin, 1992; Pertwee, 1991). However, these are both transient and mild. There is no direct pharmacological evidence to suggest that the consumption of cannabinoids would encourage the taking of any other type of drug.

2.14 Given the evidence discussed above, it is not at all unexpected that some individuals choose to self-medicate with cannabis. Clearly further research into the medicinal properties of cannabis and cannabinoids is required. However, this will take some time and, meanwhile, self-medication with cannabis will no doubt continue to occur in Britain (I have no data on how prevalent this practice is). Consequently, it seems to me that a strong case can be made on the grounds of common sense and compassion for allowing doctors to prescribe nabilone, dronabinol and/or (oral) cannabis now for serious symptoms including muscle spasms. This would seem better than the present state of affairs where many patients who in all other ways appear to be law-abiding citizens feel so strongly that they should self-medicate with cannabis that they are prepared to take the concomitant risks: the chance of discovery and punishment, the need to consort with drug dealers, the consumption of cannabis of unknown potency and pedigree that may contain microbial toxins or be adulterated with other drugs, pesticides or weed killer and the total lack of medical supervision of the cannabis consumption. For this particular issue to be addressed properly it will be important to obtain input not just from scientists and physicians but also from other specialists, including lawyers and the police.

2.15. In conclusion, there is sufficient evidence to warrant additional clinical studies with cannabinoids for the management of several disorders, including multiple sclerosis, spinal injury, glaucoma, bronchial asthma and pain. These studies should be directed at providing objective and conclusive answers to the following questions. First, do cannabinoids have efficacy against selected symptoms that is of clinical significance and, if so, do the benefits outweigh the known risks? Second, does cannabis (or a mixture of two or more cannabinoids) have any therapeutic advantages over individual cannabinoids such as  $\Delta^9$ -tetrahydrocannabinol? Third, is there a significant need for additional drug treatments to manage any of the disorders against which cannabinoids may prove to be effective? Additionally, it will be important to search for better cannabinoid formulations and modes of administration, possibilities including cannabinoid administration by rectal suppository (Brenneisen et al, 1996), by skin patch, by direct application to the eye (for glaucoma) or by aerosol inhalation (para 2.6). To succeed, clinical studies with cannabinoids will require adequate funding, the availability of appropriate outcome measures and the committed involvement of scientists and physicians with appropriate cannabinoid and clinical expertise.

### 3. REFERENCES

- Abood, M E & Martin, B R (1992) Neurobiology of marijuana abuse. *Trends Pharmacol Sci* 13, 201–206.
- Brenneisen, R, Egli, A, ElSohly, M A, Henn, V & Spiess, Y (1996) The effect of orally and rectally administered  $\Delta^9$ -tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther* 34, 446–452.
- British Medical Association (1997) *Therapeutic Uses of Cannabis*. Harwood Academic Publishers. Amsterdam.
- Chaudry, H R, Moss, H B, Bashir, A & Suliman, T (1991) Cannabis psychosis following bhang ingestion, *Br J Addiction* 86, 1075–1081.
- Chopra, G S & Smith, J W (1974) Psychotic reactions following cannabis use in East Indians. *Arch Gen Psychiat* 30, 24–27.
- Clark, W C, Janal, M N, Zeidenberg, P & Nahas, G G (1981) Effects of moderate and high doses of marihuana on thermal pain: a sensory decision theory analysis. *J Clin Pharmacol* 21, 299S–310S.
- Compton, D R, Aceto, M D, Lowe, J & Martin, B R (1996) In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): inhibition of delta-9-tetrahydrocannabinol-induced responses and apparent agonist activity. *J Pharmacol Exp Ther* 277, 586–594.
- Consroe, P, Musty, R, Rein, J, Tillery, W & Pertwee, R (1997) The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 38, 44–48.



12 May 1998]

[Continued

Dunn, M & Davis, R (1974) The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 12, 175.

Finnegan-Ling, D & Musty, R E, Marinol and phantom limb pain: a case study, *International Cannabis Research Society Abstract*, 1994, p53.

Green, K (1998) Marihuana and intraocular pressure: possible mechanisms of action. Paper presented at International Conference on Marihuana and Medicine, 21 March, New York Univ Medical Center.

Grinspoon, L & Bakalar, J B, *Marihuana, The Forbidden Medicine*, New Haven, Yale University Press, 1993.

Herzberg, U, Eliav, E, Bennett, G J & Kopin, I J (1997) The analgesic effects of R(+)-WIN 55, 212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neurosci Letts* 221, 157-160.

Hill, S Y, Goodwin, D W, Schwin, R & Powell, B (1974a) Marijuana: CNS depressant or excitant? *Am J Psychiat* 131, 313-315.

Hill, S Y, Schwin, R, Goodwin, D W & Powell, B J (1974b) Marihuana and pain. *J Pharmacol Exp Ther* 188, 415-418.

Holdcroft, A, Smith, M, Jacklin, A, Hodgson, H, Smith, B, Newton, M & Evans, F (1997) Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 52, 483-488.

Hollister, L E (1986) Health aspects of cannabis. *Pharmacol Rev* 38, 1-20.

Jain, A K, Ryan, J R, McMahon, F G & Smith, G (1981) Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 21, 320S-326S.

Jones, R T & Benowitz, N (1976) The 30-day trip—clinical studies of cannabis tolerance and dependence. In *The Pharmacology of Marihuana* (ed Braude, M C & Szara, S), pp 627-642. New York, Raven Press.

Karniol, I G, Shirakawa, I, Takahashi, R N, Knobel, E & Musty, R E (1975) Effects of  $\Delta^9$ -tetrahydrocannabinol and cannabinol in man. *Pharmacology* 13, 502-512.

Lichtman, A H, Cook, S A & Martin, B R (1996) Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther* 276, 585-593.

Lichtman, A H & Martin, B R (1991) Spinal and supraspinal components of cannabinoid-induced antinociception. *J Pharmacol Exp Ther* 258, 517-523.

Lichtman, A H & Martin, B R (1997) The selective cannabinoid antagonist SR 141716A blocks cannabinoid-induced antinociception in rats. *Pharmacol Biochem Behav* 57, 7-12.

Martin, B R, Thomas, B F, & Razdan, R K (1995) Structural requirements for cannabinoid receptor probes. In *Cannabinoid Receptors* (ed Pertwee, R G), pp 35-85. London, Academic Press.

Martin, W J, Lai, N K, Patrick, S L, Tsou, K & Walker, J M (1993) Antinociceptive actions of cannabinoids following intraventricular administration in rats. *Brain Res* 629, 300-304.

Noyes, R, Brunk, S F, Avery, D H & Canter, A (1975a) Analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 18, 84-89.

Noyes, R, Brunk, F, Baram, D A & Canter, A (1975b) Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 15, 139-143.

Paton, W D M & Pertwee, R G (1973) The actions of cannabis in man. In *Marijuana* (ed Mechoulam, R), pp 287-333. New York, Academic Press.

Paton, W D M, Pertwee, R G, & Tylden, E (1973) Clinical aspects of cannabis action. In *Marijuana* (ed Mechoulam, R), pp 335-365. New York, Academic Press.

Pertwee, R G (1991) Tolerance to and dependence on psychotropic cannabinoids. In: *The Biological Bases of Drug Tolerance and Dependence*, Ed J A Pratt, pp 231-263. Academic Press, NY.

Pertwee, R G (1996) Cannabinoid receptor ligands: clinical and neuropharmacological considerations relevant to future drug discovery and development (Invited editorial). *Expert Opin Invest Drugs* 5: 1245-1253.

Pertwee, R G (1997a) Pharmacology of cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors. *Pharmacol Ther* 74: 129-180.

Pertwee, R G (1997b) Cannabis and cannabinoids: pharmacology and rationale for clinical use. *Pharmaceut Sci* 3: 539-545.

Pertwee, R G (1998a) Some pharmacological, physiological and clinical implications of the discovery of cannabinoid receptors. *Biochem Soc Transact* 26 (2). In press.

Pertwee, R G (1998b) Cannabinoid receptors and their ligands in brain and other tissues. Paper presented at International Conference on Marijuana and Medicine, 20 March, New York Univ Medical Center.

12 May 1998]

[Continued

Pugh, G, Smith, P B, Dombrowski, D S & Welch, S P (1996) The role of endogenous opioids in enhancing the antinociception produced by the combination of  $\Delta^9$ -tetrahydrocannabinol and morphine in the spinal cord. *J Pharmacol Exp Ther* 279, 608–616.

Raft, D, Gregg, J, Ghia, J & Harris, L (1977) Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of analgesic response. *Clin Pharmacol Ther* 21, 26–33.

Regelson, W, Butler, J R, Schultz, J, Kirk, T, Peek, L, Green, M L & Zalis, M O (1976)  $\Delta^9$ -tetrahydrocannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In *The Pharmacology of Marijuana* (ed Braude, M C & Szara, S), pp 763–776. New York, Raven Press.

Rinaldi-Carmona, M, Barth, F, Héaulme, M, Shire, D, Calandra, B, Congy, C, Martinez, S, Maruani, J, Néliat, G, Caput, D, Ferrara, P, Soubrié, P, Brelière, J C & Le Fur, G (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letts* 350, 240–244.

Roth, M D, Arora, A, Barsky, S H, Kleerup, E C, Simmons, M & Tashkin, D P (1998) Airway inflammation in young marijuana and tobacco smokers. *Am J Respi Crit Care Med* 157, 928–937.

Tashkin, D P, Reiss, S, Shapiro, B J, Calverese, B, Olsen, J L & Lodge, J W (1977) Bronchial effects of aerosolized delta-9-tetrahydrocannabinol in healthy and asthmatic subjects. *Am Rev Respi Dis* 115, 57–65.

Tennant, F S & Groesbeck, C J (1972) Psychiatric effects of hashish. *Archs Gen Psychiat* 33, 133–136.

Tsou, K, Lowitz, K A, Hohmann, A G, Martin, W J, Hathaway, C B, Bereiter, D A & Walker, J M (1996) Suppression of noxious stimulus-evoked expression of fos protein-like immunoreactivity in rat spinal cord by a selective cannabinoid agonist. *Neurosci* 70, 791–798.

Williams, S J, Hartley, J P R & Graham, J D P (1976) Bronchodilator effect of  $\Delta^1$ -tetrahydrocannabinol administered by aerosol to asthmatic patients. *Thorax* 31, 720–723.

I have submitted the above evidence on an individual basis.

Dr Roger Pertwee

20 April 1998

### Examination of Witness

DR ROGER PERTWEE, Reader in Biomedical Sciences, University of Aberdeen, was called in and examined.

#### Chairman

252. Good morning, Dr Pertwee. I am deputising for Lord Perry of Walton who, unfortunately, is ill and cannot come. I wonder if you would like to introduce yourself and make any introductory comments about the International Cannabinoid Research Society?

(Dr Pertwee) I started working on cannabinoids some 30 years ago in Oxford and then moved up to Aberdeen, where I continue to work on cannabinoids. I have a team of about eight scientists in my group now, being postdocs, postgrads and research technicians. Our work is funded by the Wellcome Trust, by the National Institute on Drug Abuse, which is part of the NIH, USA, and by a drug company. We are particularly interested in developing new tools to study what is called the endogenous cannabinoid system and new drugs—agonists and antagonists—and to look for new receptor types (and we will come on to receptors later), and to study the process of cannabinoid tolerance. Also, at the human level, we are interested in looking at more clinical aspects. As a start we have set up a method for measuring blood levels of cannabinoids. So that is me. The International Cannabinoid Research Society is a scientific society—it is not a campaigning society, it is very much a scientific society—and its main object is to facilitate scientific advances in the cannabinoid field. The main way we do that is to hold annual scientific meetings where people present their latest data and

we exchange ideas. It is also a good place for people to set up scientific collaborations, which is much easier these days with E-mail than it used to be. So it is very easy for me, for example, to collaborate with medicinal chemists, particularly in the USA and, also, in Israel.

253. How many people would attend these annual meetings?

A. Between 100 and 200 people.

254. From this country or from where?

A. From all over the world. It is an international society. They are mainly from the USA, although this year we have our first ever meeting in Europe. I should say, I am the President of that society and maybe that is one reason it is in Europe. I notice with interest that there are, in fact, a lot of people this year coming from Europe rather than from the USA.

255. [unallocated]

256. Perhaps we can now go on to the main part of the discussion and ask you how the discovery of endogenous cannabinoid substances and the receptors for these helped to provide new insights into the physiological role of the cannabinoid system?

A. I would like to turn the question round slightly. It was the discovery of the receptors and of the endogenous ligands for these receptors which led to the idea that there actually is an endogenous cannabinoid system. That is how it started. Now we have that system, of course, we are interested to



12 May 1998]

DR ROGER PERTWEE

[Continued]

Chairman *contd.*]

know what its functions are. At the moment it is very much a matter of speculation. The clues we have come from the way in which receptors are distributed in the body and, also, from what we know about the pharmacological actions of drugs which interact with these receptors. The possible physiological roles of the system include involvement in cognition, learning, memory (because a lot of receptors are found, for example, in the cortex and in the hippocampus in the brain), mood, and perception. We know that cannabinoids affect the perception of various things: pain, light, sound and time. In fact, the effect on time is the opposite to that of alcohol, in that time seems to pass much more slowly in people who take cannabis. Movement and motor function. This is very important, because probably the highest concentration of these receptors is in what we call the basal ganglia—those parts of the brain which are involved in the control of movement. Appetite. Cannabinoids stimulate appetite, particularly for sweet food. In fact, that is exploited clinically, as we will come on to later. The process of sleep. Quite recently a new sleep factor was isolated from sleep-deprived cats, extracted and given to rats which show signs of sleep. This sleep factor does not interact directly with the cannabinoid system; what it seems to do is prevent the metabolism of endogenous cannabinoids and, in so doing, it boosts the function of this endogenous system. That may account for its sleep promoting effects. That is just hypothesis, at this stage. Certainly, there is a possibility of a role in sleep. Thermoregulation, endocrine function and then, on the CB2 side—perhaps also CB1—immune function. There are a lot of cannabinoid receptors on cells of the immune system, and their role there remains to be established. That is all very new stuff. The processes of inflammation and allergy. For example, there is some evidence that cannabinoids prevent most cell degranulation through their receptors. Those are some of the possible physiological roles of this system. Perhaps it is worth mentioning that overall what may be happening, on the CB1 side of things anyway, is that the system modulates the release of other chemical messengers. So when the receptors are activated, chemical messenger release is changed; usually there is an inhibitory effect—although sometimes an excitatory effect—and not one particular transmitter but a whole range of different transmitters. One example is that acetylcholine release from hippocampal neurones is reduced, and that would fit in with the ability of cannabinoids to impair memory, particularly short-term memory. So the overall function of the system may be to modulate neurotransmission, and all these other things I mentioned are as a result of that. Pharmacologically, of course, the discovery of the system has opened up new targets for drugs and these are both the receptors and, also, the enzymes and other processes responsible for the production and fate of endogenous cannabinoids. As far as fate is concerned, we are probably dealing with both the metabolism within the cell, (the enzymes are microsomal), and an uptake process, (anandamide has a neuronal uptake process). These are potential targets for drugs which can be produced to modulate the system through these targets. One other point,

perhaps, is that there is evidence that the system has tone. It is active; even if you do not give any drugs to someone the system is active. Presumably the chemicals which act on these receptors are being released. Also, there is some evidence for what we call a precoupling of receptors—some receptors for cannabinoids are already active, even though there is no agonist there. That is not unusual, this happens with other systems as well. So there is tone in the system, and one significant point about that is it means that if you give an antagonist by itself you may well see effects, and those might be of interest therapeutically.

257. Are the various effects that you have described for the endogenous substances due to a single or a small range of endogenous cannabinoids? And do the endogenous cannabinoids match the natural cannabinoids that occur in cannabis? Is there an endogenous cannabinoid for every external one?

A. No, there is not. The endogenous cannabinoids probably match tetrahydrocannabinol, which is the main psychotropic constituent of cannabis. That would seem to be the case. There is definitely more than one endogenous cannabinoid. One of the two most important ones at the moment—although there may be others—is anandamide. We called it anandamide because “ananda” is the Sanskrit word for “bliss”. Interestingly, and much to our surprise, it is a derivative of arachidonic acid—it is arachidonylethanolamide. Perhaps it is not surprising, because one of the properties of cannabinoids is that they are very, very fat soluble. The other one is 2-arachidonoylglycerol, which is present in much higher concentrations in the brain, and it is possible it may be more important. Then again, it could be that anandamide is synthesised on demand and is not stored.

*Lord Porter of Luddenham*

258. That is all very interesting. Cannabinoids do so many things. How do you see the evolutionary development and purpose of cannabinoid receptors?

A. In evolution?

259. Yes. Why did they start?

A. Your guess is as good as mine! It is a very good question. I do not think one knows the answer to that, really. They are very well conserved between species, which suggests that maybe they are quite important.

260. So it is an early thing in evolution?

A. Yes. They have been detected in fish and they have been detected in the leech, I think. I do not know how far down the chain one goes before one does not see them. I have got a vague feeling they have been seen in insects, but I cannot remember exactly.

261. And plants, presumably?

A. That is a very good question. I do not think anyone has looked for receptors in plants, but you would have thought so. Unless the material in the plant is produced to do something to insects who prey on the plant. I do not know.



12 May 1998]

DR ROGER PERTWEE

[Continued]

*Lord Dixon-Smith*

262. Dr Pertwee, clearly the science involved in both cannabis and cannabinoids and the way they work is developing very, rapidly and still has a long way to go. So perhaps you would like, in the light of that, to give us your views on the medical uses of both cannabis and cannabinoids. Is there scientific evidence which genuinely supports their use in the treatment of spasticity and pain?

A. First of all, I think I should point out there are some uses to which cannabinoids are already put. In this country, nabilone—which is a synthetic analogue of THC, which is the main psychotropic constituent of cannabis—is licensed for use as an anti-emetic, particularly to suppress nausea and vomiting produced by anti-cancer drugs. That is the only thing for which it is licensed to be used in this country. In the United States THC itself is a medicine. It is licensed for use for the same purposes as nabilone over here and it is also licensed for use as an appetite stimulant. One of its uses is to stimulate appetite in AIDS patients in an attempt to reverse excessive weight loss. Those are licensed uses. In addition to that, there are a number of potential uses to which these drugs might be put. To save time I have listed them here. I will not go through them all, there are quite a few, but the most important ones are: disorders of movement and muscle tone, including those seen in multiple sclerosis and spinal cord injury; chronic pain, particularly in neuropathic pain, of which an example might be phantom limb pain. A lot more work is needed to explore that possibility, because that is very poorly managed in the clinic at the moment. Bronchial asthma is another one, because there is evidence that cannabinoids can open up the airways, although the mechanism for that remains to be established. Another one worth mentioning is glaucoma, because there is good evidence that cannabinoids do lower pressure in the eye and might, therefore, be of potential use for glaucoma. If one had to pick the two with the greatest potential, you would probably go for spasticity and pain, which brings me on to the second part of your question, my Lord, which concerns that. There is quite good evidence, as far as MS and spinal cord injury is concerned. This comes, firstly, from what we know about the pharmacology of cannabinoids, particularly how the receptors are distributed—as I have mentioned, a lot of these receptors are in the basal ganglia. Also, we know that cannabinoids can suppress spinal reflexes, which would fit in. In addition to that, at the animal level there is an animal model for multiple sclerosis called experimental autoimmune encephalomyelitis (EAE). In EAE cannabinoids are actually very effective in reducing the intensity of the syndrome. The question is, how good a model that is of MS, but nonetheless it is encouraging. Along with that there are some anecdotal data, most recently our own data. What we did was to carry out a survey of MS patients who self-medicate with cannabis, both in this country and in the USA. We had exactly 112 replies and, to cut a long story short, well over 90 per cent claimed that they took cannabis because it reduced the spasticity, muscle spasm, and the discomfort and pain associated with that. That was the main claim. The reason we carried out that survey was to find out what these claims are, because we felt this would help

to set up a clinical trial in which we could test out these claims objectively. I do not think the anecdotal data by themselves prove very much. Obviously they do not carry very much weight in the scientific community, but, nonetheless, it is important to find out from people who do go to the bother of self-medicating in this way exactly why they take the cannabis. That is what we did. Our next step will be to carry out a clinical study. Having said that, there have been some clinical studies—I think five or six all together—mostly with THC given orally. There were three such trials: in addition there was one with nabilone in this country with a single patient, and one with cannabis—an open label study, which means, of course, the patient knew he was taking cannabis. The problem with these studies is that very small numbers of patients were used, sometimes just one or two subjects. They were mostly well controlled trials, as far as they can be with cannabinoids: they were placebo-controlled, double blind, and so on—except for the open label instance. Nonetheless, the numbers were very small. The overall message from these trials is that there was cannabinoid induced improvement in spasticity, painful spasticity, tremor, handwriting performance and nocturia—reduced frequency of wanting to urinate at night. That is the evidence so far, except for additional evidence as far as pain is concerned. There have been one or two other clinical studies (not with MS patients or spinal cord injury patients) which have looked at the ability of cannabinoids to relieve pain—cancer pain, for example, and post-operative pain. Those have yielded positive results. Again, the data are very limited.

263. You might be able to help us answer what is, in a sense, a philosophical question. Is there a point at which the body of anecdotal evidence becomes so overwhelming that, in fact, it becomes solid evidence? Or is anecdotal evidence always anecdotal evidence.

A. I am pretty convinced by the anecdotal evidence myself, but I might have a job convincing the Department of Health, for example. That is the problem.

264. This is the problem we will find ourselves wrestling with at the end of the enquiry.

A. I have spoken to many patients and many write to me, and they tell me they are getting benefit from cannabis. They are very clearly not hippies, very often, and they are risking punishment. Some of them are growing their own stuff and risking imprisonment (I am told the going rate is one month per plant, but I do not know this for certain), yet they are prepared to take that risk. I can only think they are doing that because it really is helping them. At the end of the day, I think, to convince the Department of Health we need further hard scientific evidence.

*Lord Rea*

265. On that point, you did mention that there have been several clinical trials in various countries. Can you tell me what the weakness of those trials, so far, is and why they are not sufficient to convince departments of health sceptics throughout the world? Can you spell out what is necessary in order



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Rea *contd.*]

to mount adequate scientific trials to prove or disprove the various effects of cannabinoids?

A. I think one of the problems with the data so far is the small number of patients who have been studied. I think that is probably the main thing. The other problem, I think, comes when you try and carry out a double blind study of these drugs, because clearly they do have psychotropic effects, and it would be very easy, I imagine, for a patient to distinguish between a placebo and an active drug. One needs to think of a strategy round that, because ideally you do want a double blind study. One solution would be to give a second active compound. I imagine one would be dealing, if possible, with patients who have not had cannabis before, so they are not experienced with the effects of cannabis, so one could imagine using an active control—perhaps a benzodiazepine (something which also has effects on mood, etc)—so that the patient would not know whether they were getting the cannabinoid or not. The main problem comes down to numbers. There are other practical difficulties, which I expect we will come on to later, but most of these studies were done with oral THC and that is not the best route to use, because the absorption is very variable.

*Lord Porter of Luddenham*

266. Can you tell us something about the research which is going on, if any, into improved methods of administering cannabis, alternative to smoking?

A. As you have surmised, very little research at the moment is going on in that area. To deal with smoking itself, first, it is actually a very good route of administration, in some ways; it is very effective, there is a very rapid absorption, and the patients have a great deal of control over how much they take. They learn to titrate. Of course, because of the tars in smoke it is not really a very good route, because of the possible carcinogenic effects. I know we are getting on to the possible harmful effects later on, so I will say no more about that. So it is really a non-starter, as far as medicine is concerned. Apart from that it is a very good route. Then we are left with other possibilities. One is oral administration. There are two problems with that. Firstly, the absorption seems to be very variable from patient to patient. That is made worse by the evidence that there seems to be a very narrow therapeutic window. You stray very rapidly from an ineffective dose, through an effective dose, into a dose which starts producing adverse effects. So you have a narrow window and you have variable absorption. That creates difficulties, so we need to find other routes of administration. One possibility is to go to the other end of the body and use a suppository. That may not be too popular in this country but I think MS patients would be prepared to do that if it did the job. An experimental version is available in the States and a colleague of mine has produced a suppository, THC-hemisuccinate, which is absorbed quite rapidly from the rectum and is then converted to THC. There is very limited data on this, as far as the pharmacokinetics are concerned, but there is some suggestion from the data that the absorption is more reliable—you also get less of an initial spiking than

you get with THC—you do not get such a rapid absorption, which I think is another problem with oral THC. Possibly it is much more reliable, but more work is needed with that preparation. Another possibility would be to use an aerosol—not a smoke aerosol but some other kind of device—to aerosolize the material. There were two studies done in the late 1970s, I think, one in this country and one in the States, and certainly it is a possible route. Both those studies showed that cannabinoids can be given in that way. One of the main problems was getting the right vehicle, but that was a long time ago and I think there are better vehicles available now. Another route is the eye, particularly for glaucoma. There is evidence that these drugs are absorbed if applied directly to the eye. Again, the problem is vehicle, and human studies have been carried out which have not been too successful because the vehicle produces a lot of “tearing”—formation of tears—which tends to wash away the drug. Again, that is a matter of vehicle, I think. You must remember, these drugs are very fat soluble and this creates the problem. Then there are other possible routes one needs to consider, finally: skin patches, possibly; slow release oral administration, so a slow release preparation; and formulation for buccal absorption. It has been shown in a study in Israel, for example, that delta-8-THC (which is also a natural cannabinoid which is active and acts through the same receptors as delta-9) is absorbed when it is placed under the tongue, in children. Interestingly enough, in these children, there were, apparently, no psychotropic effects. That has been put down to the age of the patients rather than to the drug.

*Lord Rea*

267. If there were not psychotropic effects, what effects were the children getting?

A. It was given to children who had cancer to suppress the nausea and vomiting produced by the therapy. I think those are the only routes. There may be other routes, but I do not know of those.

*Lord Porter of Luddenham*

268. Do I understand that the advantage of inhaling cannabis—smoking—is that the partaker can control it much better? Is that because the action happens so quickly, whereas if there is a long delay then you go on, presumably, taking it by whatever method you have?

A. Yes, when the drug is taken by smoke or when it is injected intravenously (which has been done experimentally) the effect comes on very rapidly. The plasma levels peak after about three minutes and the effect peaks within ten minutes. So they have very rapid feedback. However, when it is taken orally you have to wait half-an-hour or an hour before you feel anything.

269. Following that, where do inhalers come in here? Do they act quickly, in the same way as smoke inhalers, aerosols and that sort of thing?

A. Yes. That is why I said one possible device would be an aerosol.



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Porter of Luddenham *contd.*]

270. They do not have the disadvantage of the other methods, which are so hard to control?

A. Indeed. I think some kind of vaporiser could be a very good mode of administration

271. Has there been any research?

A. There were two studies in the 1970s using a nebuliser and certainly it was effective—the drugs were absorbed and had an effect—but the problem was the vehicle was tending to produce effects itself. One needs a better vehicle.

272. What, the solvent?

A. Yes. The alternative would be to vaporise the material without any vehicle at all, I suppose, but I am not an expert on that side of things. Some kind of heating device.

*Lord Rea*

273. Just a follow-on from that question on vaporisation and nebulisation, are some of the components of natural cannabis perhaps more volatile or more easy to put into a nebuliser than others?

A. I was thinking, as I was speaking, of a single cannabinoid, particularly THC, but I suppose theoretically it would be possible to do it for a mixture and, indeed, for an extract of cannabis. However, I do not know how the various constituents would take to that.

274. How important are the long half life of THC in the body, and the formation of active metabolites by the liver, in determining the nature and duration of its pharmacological action and effects?

A. I am not a pharmacokineticist, but, nonetheless, I have done my best to come up with an answer. The pharmacokinetics of THC are rather complex. When THC is smoked or taken intravenously it peaks very rapidly in the blood and then disappears quite rapidly, initially. So we are talking about a 50 per cent reduction in plasma level in ten minutes. So it is falling off very rapidly initially. The high which is experienced along with it—the psychotropic effects—tend to lag a bit behind that, which is what you might expect, because although the plasma levels are falling the levels in the brain are still going up. Then they reach a plateau and come down again. However, you cannot measure levels in the brain directly, only those in plasma. There is this lag of half-an-hour or so, but eventually, too, the psychotropic effects come down in parallel with the plasma levels, but lagging behind. After about three or four hours you reach very low levels of THC in the blood. Then, at that point, the THC disappears very slowly, and we are talking then about a terminal half life, because there seems to be a multi-compartment system—it is not just a single exponential, there are several exponentials, or components, to this. With the terminal half life effect, we are talking about 26 or 30 hours, so that is a very, very slow disappearance. So it is starting at a level at which, probably, you cannot detect any pharmacological effect anyway; so you are getting this very slow disappearance of what is already a very low level of THC.

275. You have described the first part of the half life but there is the long, long tail. That, I believe, can be detected for up to 30 days.

A. At very small levels in rats that has been demonstrated, yes.

276. This is one of the problems in testing for cannabis use in drivers. Would it be possible to say that it would be having an effect at a certain level which would be before that long tail?

A. There have been studies carried out where they have followed the changes in the blood level and looked at things like pulse rate, self-perceived high and psychotropic effects. Another useful indicator is the colour of the eye; you get a reddening of the eye with cannabis, and that tends to disappear as the level of the drug goes down. In these studies, when the drug was given either by smoke or intravenously, the effects became undetectable after about three or four hours before the terminal stage was reached where, as I was saying earlier, it starts to disappear very slowly. So at the point at which it is disappearing very slowly it already has a negligible effect. If you had a very sensitive test, no doubt you might be able to pick something up, but just using the kind of tests I mentioned nothing was detected at that point.

277. There is work going on in trying to develop a suitable test for drivers. Can you tell us a little bit about how far that has developed?

A. I am sorry, I do not know anything about that side of things.

278. What about these active metabolites?

A. THC is initially hydroxylated to a number of different hydroxymetabolites. Perhaps the most important one is what is called 11-hydroxy-delta-9-THC. It is metabolised mainly in the liver, and what is interesting about this metabolite is that it is pharmacologically active and, indeed, there is good evidence that it is more active than the parent compound. This is an unusual situation where a drug is actually metabolising to a more active compound. Of course, that metabolite goes on further to other metabolites, and those are inactive. We go through a period where THC is producing a compound which is more active than itself. It is difficult to put a figure to that, as of course if you give THC to an animal you are going to get the effect of THC plus its metabolite, and it is difficult to separate out the two. Nonetheless, if you do in vitro studies, where the THC is not being metabolised very much, you are talking about a 3, 4, 5-fold difference in activity—the hydroxymetabolite being 3, 4, 5, 6, 7 times more potent than the parent compound. So there is a significant difference in the potency. So the effect of the THC, when it is given in vivo, is going to be, to some extent, due to the metabolites that are formed, and there are one or two other hydroxymetabolites which are also active, but probably less potent than the 11-hydroxy, I think. What is interesting is that the ratio of the parent compound to the metabolite varies, depending on the route which is used. If a drug is given intravenously we have something like ten times as much of the parent compound as of the metabolite—so very little metabolite when the drug is taken by smoke or intravenously. On the other hand, when the drug is taken orally we have, maybe, twice as much



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Rea *contd.*]

metabolite as parent compound. So the metabolite has a greater role to play when the drug is taken orally than when it is smoked or given intravenously. The probable reason for that is that when the drug is taken orally it goes straight to the liver, where it is metabolised, whereas when smoked or given intravenously it misses out "first pass" metabolism by the liver, and so you get that difference. As far as I know, THC and metabolites have the same mode of action; as far as I know they interact with the same receptor and in the same way, but of course the metabolites, by their very nature, are more polar than THC (parent compound). Whether that means that they are distributed differently, I do not know, but that is a possibility; because they are more polar they, maybe, get to those parts which THC does not get to—to coin a phrase. It may result in subtle differences between the effect of THC by these different routes because of the differences in pharmacological activity and polarity between THC and its metabolites. As I say, because the metabolite is more active and polar there may be different overall effects.

Chairman

279. Can I ask about heavy cannabis users? They may accumulate THC in the fat tissues. Can this have adverse consequences on long-term metabolism?

A. I do not know that. There have been studies where monkeys were exposed to very high levels, by smoke, of cannabinoids for a six-month period, I think. When they looked for functional changes in the brain they could find absolutely no functional changes at all. The answer to your question is that, probably, no one knows, but it would seem that, as I say, although THC remains in the body for a long time it is at very low levels, so whatever long-term effects there are would have to be effects in systems which are particularly sensitive to cannabinoids.

280. On the question of cannabinoids being stored in fat, suppose one goes on a fast, or a diet where fat reserves are lost very quickly. Can the release of cannabinoids from fat tissue, in those circumstances, be dangerous?

A. That is a very interesting question, to which I do not know the answer, my Lord Chairman.

Lord Porter of Luddenham

281. What new research strategies are there in the cannabinoid field which might help to dissociate—very important if we could—the medical and psychoactive effects of these substances?

A. One solution is to avoid the issue altogether, and that is to go for drugs which interact with the CB2 receptor, which is the one which, according to general opinion, is not found on neurones. There is one publication which suggests that these receptors are on neurones, but no one else has shown that, as yet. So you avoid the issue by going for drugs which activate CB2 receptors, but the question is what they would be used for, and present knowledge on this is at a very early stage. Drug companies, I think, would love to see the science move forward on that, and I think that is a very important area to fund because

there could be lots of interesting uses which involve the CB2 side of the system and, therefore, avoid the "high". Another way of avoiding it is to work with antagonists rather than agonists.

282. This is the question of whether there are therapeutic uses for these recently developed cannabinoid receptor antagonists.

A. As far as that side of it is concerned, there is good evidence that there is tone in the endogenous cannabinoid system. As I mentioned earlier, it is active without there being any cannabis present or any cannabinoid receptor agonist present. There seems to be on-going release of endogenous cannabinoids occurring naturally, which is what you would expect if a system has a physiological role. Also, some of the receptors are already active even when there is no agonist there. That being the case, one would expect the antagonist to have an effect by itself, and there is certainly evidence that these antagonists do. There is evidence from a study with rats that they can improve memory, and this raises the possibility that antagonists—particularly CB1 antagonists—might be used for treating memory disorders and disorders of cognition—possibly even some of the symptoms of Alzheimer's disease. If you look through the patent literature that is one of the effects which is listed along with these antagonists. Other ones are psychoses—the treatment of schizophrenia. One of the possible adverse effects of cannabis, which we will come on to later, is that it can precipitate schizophrenia—paranoid delusions and so on—and that has raised the possibility among drug companies that an antagonist might be useful in treating certain kinds of schizophrenia. That is listed and appears in the patent literature. Another one is appetite. Cannabinoid receptor agonists stimulate appetite, so perhaps antagonists will block or reduce appetite, particularly for sweet food. You can imagine a drug company would like to produce a drug which may stop people going for chocolates and sweets. That sort of thing would sell well. That is down in the patent literature as well. In fact, I have just seen a paper in *Current Contents* this week which claims to have shown that the antagonist reduces the consumption of sweet foods by rats. So those are the sorts of things for antagonists.

283. These are all exciting possibilities or ideas, but what achievements are there? In your opinion, in a field like this, is there enough research going on?

A. No, there is never enough research going on. There is always a need for more funding to do more research. I think, in particular, on the CB2 side, we need more funding on that subject—the immune side. I think that could be very exciting, because these receptors are present in large amounts in the immune system and we do not really know why they are there.

284. If you have a fixed amount of money, where would the sort of research you are talking about rate in competition with other demands?

A. I think it should rate very highly, my Lord, but others might disagree. You will remember, from your time, what it was like, I am sure.

285. You really do think this should have a pretty high priority?



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Porter of Luddenham *contd.*]

A. I think so. After all, it is a newly discovered system in the body. We all have our own cannabis, if you like—whether we like it or not. What is it doing there? Why do we have this system? Why do we have all these receptors? CB1 receptors are present in very, very high concentrations in the brain—higher than many other receptor types—yet we know very little about it. I should say that the CB1 receptor was only cloned in 1990 and CB2—you will be pleased to hear, in Cambridge, in the United Kingdom—in 1993. So it is all quite recent stuff. So is the discovery of the endogenous agonists; 1992 for anandamide and 1995 for the other one. Returning to antagonists, the reason we have antagonists is because a drug company has developed them. A drug company, called Sanofi, is very interested in cannabinoid systems, particularly antagonists. They developed the CB1 antagonist in 1994, and then last year, at our annual meeting, they announced the CB2 antagonist. The CB1 antagonist is undergoing phase one clinical studies at the moment, I believe.

Lord Rea

286. Could you repeat the name of the drug company, please?

A. The name of the CBE antagonist is SR141716A, and the company is Sanofi.

Lord Porter of Luddenham

287. Would such an antagonist acting on the CB2 receptor put it completely out of action for all the many things that it does?

A. Acting on the CB1 receptor, it would do that, presumably.

288. It will put it out of action for all purposes?

A. There are two receptors, CB1 and CB2, but so far there is no evidence of sub-types of CB1, so the antagonist will block all the CB1 receptors throughout the body, yes.

289. And all the very different actions we have referred to?

A. Yes.

290. CB2 is different?

A. CB2 antagonists will block all CB2 effects but not CB1 effects; it is selective for CB2. What CB2 antagonists might be used for remains to be seen because, as I said, we need to carry out more research into the CB2 side. No one really knows. Even the drug companies do not know, although they have an antagonist, what to do with it at the moment.

Lord Rea

291. Am I right in thinking that each receptor is fit for one particular molecule? So that, therefore, one of the endogenous cannabinoids has, possibly, multiple effects, rather than that you have several closely similar compounds, each with a different effect?

A. The endogenous compounds that have been discovered so far will bind to both CB1 and CB2 receptors. What is interesting about anandamide, which is one of the endogenous cannabinoids, is that

there is some evidence from Professor Mechoulam's laboratory in Israel that when the anandamide interacts with the CB2 receptor it does not produce much of a change—it is what we call a partial agonist. It has affinity for the receptor but it does not have very much efficacy, so when it binds to the CB2 receptor it does not do very much. Other people have shown, however, that when anandamide binds to a CB2 receptor it does do something, and that remains to be sorted out.

292. With anandamides, part of the molecular structure locks on to the receptor. Do you have a variable other part?

A. The process of the drug receptor interaction has, really, two stages to it. One is the binding of the drug to the receptor, which both an agonist and an antagonist can do. Then there is a second component, which is to trigger a series of changes which result in responses that you can see. It is not an "all or nothing" thing for agonists; some agonists are very good at doing that, when they interact with a receptor, and others are very weak at doing that. So that if there are not many receptors there in the first place you may not see any effect at all. It is all getting a bit technical, I am sorry, but it is possible, therefore, that although anandamide can interact with both receptor types its effects are mainly going to be through the CB1 receptor.

293. I may be a bit slow here. Is it just, as far as you can tell, one chemical structure, or are there various add-on bits to anandamide which might make it more effective in one respect or another?

A. In fact, there are two minor, probably, metabolites of anandamide which are also active, but they are structurally very similar. On top of that there are a whole lot of synthetic anandamide analogues, but those are ones which have been produced in the laboratory and are not found naturally.

Lord Butterfield

294. Presumably you would have to do clinical investigations to follow up this research; it is not something you can do in animals because, presumably, it is very difficult to find out what animals are thinking or what is going on in their brains. Is this an indicator of a need for clinical investigation?

A. There is a need for both clinical and preclinical. As far as preclinical is concerned, we need to find out more about the CB2 system, and that can be done, probably, using cultured cells or animal tissue—that sort of thing. In addition, of course, to move the clinical side onwards, for example, to explore the potential of cannabinoids for multiple sclerosis, one needs more clinical studies, yes.

295. From the pharmaceutical companies' point of view, they would presumably be more interested in knowing there is something happening clinically than putting a great deal of money into phase 1 studies in animals?

A. The problem with the CB2 side of the story—the immune side—is that really we do not understand what the CB2 receptor is doing on the immune cell. We do not know what its function is. Really, I think,



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Butterfield *contd.*]

before proceeding to very expensive clinical studies one needs to do the basic science. The science is behind at the moment, unfortunately. I think the drug companies are dying to get in there but they do not know what to do, or how to exploit the CB2 system.

Lord Dixon-Smith

296. It sounds to me as though it is the most wonderful field of work which has got endless possibilities.

A. There are actually other approaches which I have not mentioned yet. Do you want me to mention those quickly?

297. [Unallocated]

298. By all means.

A. We got hung up on the antagonists but there are other possible approaches to avoid the psychotropic effects of cannabinoids, theoretically anyway. One is to develop what is called a partial agonist which is a drug which will tend to have a cut off effect. This is the sort of thing I was talking about with anandamide. It is a drug which will bind to the receptor and does something but not very much when it interacts with the receptor. What tends to happen there is you reach a ceiling. Codeine is an example in the opioid field. Codeine can relieve at its maximum dose only relatively modest pain. No matter how much more codeine you give you cannot relieve more severe pain, you need to go to morphine or a drug which has a higher efficacy to get an effect. One solution then would be to develop a drug which is a partial agonist of this kind which has a low ceiling to its effect so that no matter how much more of that drug you give you do not get a more intense effect. Ideally of course that would be a drug which did not reach its ceiling for the sought after effect but did reach its ceiling for the effect one did not want. That is a bit of a gamble and of course that might not happen. At the end of the day it would depend on the concentration of the receptors in different parts of the brain because this drug would act more in those parts of the brain where there were lots of receptors than in those parts of the brain where there were relatively few receptors. We do have such a drug because we found one last year, there is such a drug sitting in our freezer. Work with this drug was done very much at the animal tissue level, and not done at the human level. Drug companies do not like this sort of drug because it is very unpredictable and it is very much a long shot. Nonetheless it is a possible strategy. Another strategy would be to develop drugs which modulate levels of endogenous cannabinoids by blocking their neuronal uptake, or blocking their metabolism. An analogy there would be antidepressants which are used in exactly the same way. When you treat depression you do not give a drug which activates noradrenaline receptors, you give a drug which blocks the uptake or the metabolism of noradrenaline or 5-HT, drugs like prozac. One can imagine developing similar drugs for the cannabinoid system and the advantage of that is you might get a more selective effect because you are only going to get an effect in those parts of the body where there is on-going release taking place. If there is no

on-going release of your chemicals you are not going to be able to modulate their levels because they are not being released in the first place. So that is another possibility. There are three other ones. One is to go for drugs which do not get into the brain at all but can interact with the CB1 receptor. They do not cross the blood brain barrier. There are analogies for other types of drugs of this sort. You may ask "Well why do you want a drug which can activate CB1 receptors only outside the brain because all the effects of interest may be within the brain", but one possibility would be to treat certain gut disorders, for example, because there are CBI receptors on the nerve terminals in the gut and we know that cannabinoids reduce the gut motility, so maybe there is a possibility there. Then there may be other peripheral effects of cannabinoids we might want to exploit and of course, if the drug did not get into the brain, one would avoid the psychotropic effects. Another one is synergism that exists between cannabinoids and certain other types of drugs, for example between cannabinoids and opioids for pain relief. If you give cannabinoids and opioids together there is evidence from animal studies and also from one human study which I mentioned in my evidence that you get a synergistic interaction. The hope there is that you get synergism for pain relief but not synergism for the unwanted central effects which might mean you could give a low dose of an opioid like heroin pethidine or morphine or whatever, and a low dose of your cannabinoid together to get the sought after effects without getting other effects. That is another possibility. There are synergisms also between benzodiazepines and cannabinoids for effects on motor function. The two together give very marked synergism for depression of motor function and if that did not spread to the other effects again you might want to exploit that. Finally, this is something we would like funding for but it is so speculative, I believe it was Lord Porterm who I saw once on television putting it this way it is "something you have to do behind the fume cupboard", that is to look for additional types of cannabinoid receptors. We do have some evidence in the literature, very preliminary evidence, that such sub-types do exist or that new types do exist. That is something we would really like to do because I think that might result in something quite useful therapeutically. We might then have a receptor which mediates something we want not something we do not want. Of course the same hope exists for the opioid field but without much success at the moment. It is all very speculative. Even so, some of us feel it is worth trying.

299. What do you see as being the adverse effects of particularly long term cannabis use?

A. Like all drugs cannabinoids have adverse effects, this is not unusual. I do not know in fact of any drug which lacks adverse effects so it is to be expected. The first obvious ones to get out of the way are the psychotropic effects, we are dealing here with medical rather than recreational use, of course recreationally that is the *raison d'être*, the "high" is not an adverse effect for recreational use, that is why people take it. Clinically presumably it is an adverse effect. More specifically, there is impairment of cognition, impairment of memory, alteration of



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Dixon-Smith *contd.*]

perception, changes in mood. The extent to which these effects will affect, for example, the operation of dangerous machinery, driving cars and that sort of thing, I think really has to be looked at more closely. You would have thought that there would be quite dramatic effects. At the end of the day I think it has been quite difficult to demonstrate very much impairment, I am sure there must be impairment, it is a matter of looking at that more closely. It is not really my area. Other effects: increased heart rate, it sounds trivial but the increase can be quite dramatic and clearly a hazard to people with disorders like angina and they should avoid that kind of effect. Then there is some anecdotal evidence that people who take cannabis can experience transient paranoid delusions which of course is a bit alarming. This is the sort of thing which you would see in a schizophrenic. The anecdotal data suggests that when that does happen the people who have taken cannabis feel that everyone else in the room is against them—the experimenters watching them all seem to be plotting against them. That is very much anecdotal. Anecdotally also that effect seems to be a reversible effect which disappears as the other drug effects wear off. Perhaps more important is some epidemiological data which you probably heard about from Professor Griffith Edwards who is much more knowledgeable on this type of thing than I am. There is some evidence that cannabinoids can destabilise people who are schizophrenic, particularly for example latent schizophrenics, people who are predisposed to schizophrenia. If they take cannabis there is some epidemiological evidence that schizophrenia may be precipitated by the cannabis and that is of course rather alarming as well. It is a matter of debate as to whether this would happen in healthy people who are not predisposed to schizophrenia, I do not know the answer to that, I do not think anyone does. At the end of the day you are faced with epidemiological type data and it is very difficult to prove a cause and effect relationship between the data which you are looking at on the one hand for the taking of cannabis and on the other hand the incidence of signs of schizophrenia. It is really outside my expertise to attempt to interpret that. Another effect may be on the unborn foetus. I think there is some evidence for reduced birth weight in children or animals born from mothers who have been exposed to cannabis.

Lord Rea

300. In studies or observations like that, how is it possible to disentangle the effect of tobacco smoke which most people take in with their cannabis resin?

A. In the human studies probably it is not possible but in the animal studies where you are injecting the material rather subjects getting them to smoke, then you can. There is animal data as well.

301. That does reduce the size of the litter?

A. Yes, produces reabsorption of the foetus.

302. The offspring, the embryos are smaller, are they?

A. I believe so, yes.

Lord Dixon-Smith

303. I do not know if there are any other comments you want to make on adverse effects?

A. Sorry, the only other thing I should add is when cannabis is smoked it is self-evident that there is probably a risk of cancer from the tar that is in the smoked material. There is some evidence from the literature that pre-cancerous changes can be detected in lung tissue from animals who have been exposed to cannabis smoke. The general opinion is that this comes from the tar they smoke not from the cannabinoids themselves.

Chairman

304. How good is the evidence that tolerance occurs in human subjects? Does it develop to all the pharmacological effects or only to some of them?

A. The first point to make here is certainly it is possible to induce tolerance to cannabinoids in man. Probably the best study was the one carried out by Reese Jones back in the 1970s. His aim was just to answer that very question, can tolerance develop? So he actually exposed his subjects to very high levels of cannabinoids to see whether the answer was yes or no. I have noted down here what he did. He gave THC, 70 milligrams a day, which is quite a big dose, at 10 milligrams every four hours and then 20 milligrams on top of that at bedtime. Later it went up to 210 milligrams a day, enormous doses over 30 days. When he did that, gave these very high doses, he saw very clear signs of tolerance. Tolerance to effects on mood, memory, EEG, sleep, heart rate, blood pressure, body temperature and so on and to performance of psychomotor tasks also. Certainly tolerance can occur, the question is whether from the medical point of view it is clinically significant. Would it occur using a dose regime used in the clinic. I do not think anyone knows the answer to that. Before going on to another point, the mechanism underlying the tolerance is not known, other than that it is probably pharmacodynamic rather than metabolic, in other words it is probably due to a reduced sensitivity to the drug rather than to a change in the way it has been metabolised or distributed in the body. There is a good chance it is due to a change in the receptor, possibly to a reduction in receptor number or to an internalisation of the receptor, the receptor is moving from the membrane into the cell. The main point I want to make is that the tolerance is probably at the level of the receptor and is not metabolic tolerance. Then you asked about the tolerance developing to all effects. We know from animal studies that tolerance develops to different effects of cannabinoids at different rates. If I give THC to a mouse and measure its body temperature, on the first day if I give enough THC I will get a big fall in temperature but the next day if I give the same amount of THC I will see a much smaller fall in temperature so some tolerance has already developed after a single largish dose of THC. After a few more injections we will not be able to detect any fall in temperature at all. Tolerance can develop very rapidly in animals to some of the effects. For other effects, however, tolerance takes longer to develop. Tolerance does not develop at an equal rate



12 May 1998]

DR ROGER PERTWEE

[Continued]

Chairman *contd.*]

to all effects. Why that should be is a matter of speculation, it could be put down perhaps to differences in receptor density in different parts of the body or to differences in the extent to which the receptors couple functionally, the coupling efficiency, as we call it, of the receptor, the extent to which it can convert the drug receptor interaction into a response. Again that is getting rather technical. In any case the tolerance seems to vary depending on the effect you are looking at. Whether there are effects to which tolerance does not develop, I do not think anyone knows, it is very difficult to prove a negative. I will speculate that if there are, these may be effects of cannabinoids not mediated by the receptor. We know that cannabinoids for example can affect the activity of some enzymes, perhaps tolerance will not develop to that, that has yet to be investigated but it is a possibility. As I say it is difficult to prove a negative.

*Lord Butterfield*

305. Can I ask you to explain your present understanding of cannabis as a drug of addiction?

A. There have been human studies on this as well as animal studies. Again if you really try hard you can demonstrate signs of withdrawal in human subjects. In other words if you give THC for a long period of time at reasonably high doses and then stop you will see signs which were not there to start with, you precipitate signs of withdrawal. The sort I have listed here—again I think this was a study by Reese Jones in the USA—are restlessness, tremor, mild nausea, hot flushes and sweating. These are mild, relatively minor symptoms I would say, and transient, they disappear over time. The other point to make is that from animal studies the intensity of the withdrawal syndrome seems to depend, as you might expect, on the dose of the drug given before withdrawal and on the frequency of that administration. Really how clinically significant this will be remains to be seen although of course it is a cause for concern that you might induce dependence but it is not clear that you necessarily would, it would depend on the dose and frequency of administration.

306. Do we know if people who do withdraw and get some of the symptoms, the tremor or salivation, and then take the cannabinoid again, can reverse the adverse effects of withdrawal?

A. I think that is very likely. I do not know if that has been done but you would expect that.

307. Do the new cannabinoid antagonists provided any fresh insights into this question of addiction?

A. It was always seemed very likely that the antagonists would have an effect in animals which were treated for some time because it was speculated that the reason the withdrawal syndrome was quite mild was because cannabinoids are very lipophilic, very fat soluble, so although they do not sit on the receptor all the time it takes a long time for them to disappear from the vicinity of the receptor. They are, as it were, suppressing their own withdrawal syndrome over a period of time by constantly going back on to the receptor again, disappearing only very slowly from the region close to the receptor.

308. Cells very often have fat droplets in them, I am just wondering whether the cannabinoids are found in any of those fat droplets.

A. I would have thought it was very likely but I do not know the answer to that. All I know is for quite a long period of time the THC will remain in the brain at quite low levels. After a single injection the THC is still detectable at very low levels after about 30 days or so. Presumably one of the places it does get to are those fat droplets. As to the withdrawal symptoms, they are not very marked, probably because the cannabinoid is suppressing its own withdrawal syndrome, it is not disappearing rapidly from the receptor—it is hanging around for a long time. Now if you give an antagonist then a different thing happens. You are suddenly stopping the action of the drug, you are blocking the receptor and you are doing it very suddenly. When you stop giving the drug, it is a very slow gradual process but here we have a very sudden event. Then what happens, and this is very exciting, you can precipitate very marked withdrawal signs, this is in animals. In one example I have here, a rat was given THC twice daily for a week, 15 milligrams per kilo IP for a week.

309. One rat, 15 milligrams to a single rat.

A. 15 per kilo, divide that by four, it is still quite a lot but divide it by four. After that week the antagonist was given and it precipitated very marked signs of withdrawal. The examples were very interestingly wet dog shakes, that was one of the signs, the animal shakes like a wet dog and fragmentation of organised behaviour was the other one which was noted. What that meant was that the animal could not make up its mind what it wanted to do, it started doing one thing and then stopped and did another thing. It started maybe scratching then it would stop and do something else.

310. Sounds like me!

A. Fragmentation of organised behaviour. The wet dog shakes were interesting because that is a typical sign of opioid withdrawal also. The antagonist has been very useful from that point of view, demonstrating that a marked withdrawal syndrome can be induced. Of course that is not probably clinically relevant since it is very unlikely that the antagonist would be given on purpose to a patient who has been receiving a course of cannabinoid receptor agonist.

311. Can you comment on the evidence that THC activates both dopamine and opioid systems in the brain?

A. It is not really my area but I will have a stab at it. First of all, there is evidence from rat studies that cannabinoids, particularly THC and a synthetic analogue developed by Stirling Winthrop called WIN 55212-2—THC and other cannabinoid agonists can increase dopamine release in the nucleus accumbens. That was first shown in the early 1990s and more recently last year by an Italian group. What is interesting is, as you might expect, firstly that the effect can be blocked by the cannabinoid receptor antagonist. You might expect that, THC is a CB1 agonist so it acts through CB1 receptors. It is also interestingly enough blocked by naloxone which is an opioid receptor antagonist. That points to a link



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Butterfield *contd.*]

between the cannabinoid system and the opioid system. Heroin will do the same thing. If you give heroin to rats it will increase dopamine release from the nucleus accumbens. That effect is also blocked by naloxone, which you might expect, since naloxone is an opioid antagonist, but not by the cannabinoid receptor antagonist. Thus the cannabinoid effect is blocked both by naloxone and by the cannabinoid receptor antagonist but the heroin effect is blocked only by the opioid receptor antagonist not the cannabinoid receptor antagonist. Increased dopamine release in the nucleus accumbens is also produced by a whole lot of other types of drugs of dependence. Many drugs of dependence seem to have in common this ability to increase dopamine levels in the nucleus accumbens. Cocaine does this, amphetamine does it, the opioids do it and now it would seem the cannabinoids do it as well. The question is how predictive that is of a drug of dependence and I do not know the answer to that. All I know is that there is an association between the two effects. I think it remains to be established that it is predictive of drug dependence. Perhaps related to that it is worth pointing out that whereas for most of these other drugs of dependence it has been very easy to persuade animals to self-administer, you can train them to press a lever for example to take the cocaine, in other words you can get them psychologically dependent on these compounds. It has been very, very difficult to persuade animals to self-administer cannabinoids, in fact I would say up to now impossible although I believe there is a paper about to appear which does describe self-administration of a cannabinoid by animals. However, I have only seen the title, maybe things will change. In the past anyway it has been very difficult to persuade animals to self-administer cannabinoids and yet easy to get them to self-administer established drugs of dependence. Going back to the effect on dopamine release and to the link between cannabinoids and the opioid system there is some evidence from work with the spinal chord that one of the effects of cannabinoids acting through their receptors is to release endogenous opioids. Compounds, like enkephalins, can be released, and maybe that is what is happening in the brain also, the cannabinoids acting on their receptors to increase the release of endogenous opioids. This could be part of the general function of the endogenous cannabinoid system which remember is probably to modulate the release of a whole lot of different chemical messengers. It could be that the opioids are just one of those and dopamine another perhaps via the opioids. We should remember that it is not the same to give an animal heroin as to give it THC. If you give an animal heroin it is going to act on all the opioid receptors in the body. The chances are if you give it THC, the THC is going to act on its receptors and maybe in one part of the brain it will increase opioid release but in another it is going to have no effect at all on opioid release. The effect is going to be more selective I think but that is guess work at this stage. I imagine it is going to be a more selective effect than giving an opioid agonist directly.

312. Are you now in a position to label cannabinoids or opioids and give them to animals

and then sacrifice the animal and take sections of the brain to see if they have picked up? Is that one of the lines of research that is going on?

A. It is possible to label the receptors with radio labelled probes. In fact that was what really led on to the discovery of the receptor in the first place. That happened in the late 1980s and it has been possible to use that approach to map out where the receptors are.

Lord Butterworth

313. In your excellent paper you bring your pleadings together by saying "A strong case can be made on the grounds of common sense and compassion for allowing doctors to prescribe nabilone, dronabinol and/or (oral) cannabis now for serious symptoms including muscle spasms." As you know we have had a lot of anecdotal evidence from those who self-medicate with cannabis that they have found natural cannabis more effective than what I might call synthetic products. How can we justify recommendations which if followed result in the normal procedures for the registration of new medicines being circumvented?

A. I will preface my answer by saying that I regard myself as a scientist rather than as a campaigner. I think this is very important, as I do not think you can be both. Given the choice I want to be a scientist. If you try to be both you will not be regarded as an objective scientist nor will you be a very effective campaigner, you have to be one or the other. So, I am speaking as a scientist today. Having said that I am very concerned by what is happening at the moment which is that there do seem to be a lot of people who self-medicate cannabis. I do not know how many, I do not know if that figure is available. I do know I get contacted a lot by solicitors and barristers who are defending clients who are self-medicating. It seems there is a problem. I think the problem is as much ethical as scientific and I am not an expert in ethics unfortunately. I will try and say what is in my mind. I think the problem then is that there are people who self-medicate with cannabis, for example for multiple sclerosis and spinal injury and presumably they believe they are doing themselves some good. They believe also—my impression is—that drugs which are available to them are not working and sometimes when they do work they have very unpleasant side effects which cause them to stop taking those drugs. That is their story anyway and I have no reason to disbelieve them. What are we going to do about it? One possibility is to prosecute them and send them to prison, that happens to some extent. Okay, that is one solution, it is not my solution but it is one solution. Another is to turn a blind eye and my impression is that happens to some extent but it depends on where you live in the country. There is great inconsistency and I really do not think that is very satisfactory, my Lord, you are the lawyer but it seems to me that is not good.

314. I agree.

A. It is bad for the law. Another possibility is to extend the licensing of cannabinoids, this is something which needs to be looked into. I think it should be possible to extend the licence of nabilone



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Butterworth *contd.*]

so that it can be used not just as an anti-emetic but also, for example, for MS. That would be feasible, I think. I do not know who would do that, whether it would be the drug company who would have to apply, I imagine that would be the situation. That is a possibility. Another one is to encourage doctors to prescribe nabilone and/or THC now for MS. Some doctors do that already for nabilone and they are entitled to do that because although nabilone and THC are not licensed for MS, or pain or whatever, it is permissible for a doctor to do this as long as the drug is not a schedule one drug, THC certainly is schedule two and nabilone is a licensed drug. It is possible for a doctor on a named patient basis if he so chooses to prescribe both these drugs for MS. Maybe doctors should be encouraged to do that. That is possible without changing the law. Another possibility of course would be to allow patients to take cannabis. I think that is probably difficult to justify until we have ruled out THC and nabilone as possibilities. Having said that, we should remember that cannabis was a medicine in this country until as recently as 1971, it was available as tincture of cannabis, for oral use. We should remember also that in a Home Office report, the Wootten report of 1968, when cannabis was still legal as a medicine, one of the final recommendations was that cannabis should remain as a medicine. This committee saw no reason why it should cease as a medicine. They probably saw no reason why it should be given as a medicine either because at that time the possible link between cannabinoids and multiple sclerosis had not been made. To be fair at that time there was no obvious reason for keeping cannabis on as a medicine. My guess is, but I do not know this, perhaps someone in this building does, that cannabis was made illegal as a medicine not because it was considered a dangerous drug but because it was considered to have no real positive value. There was no obvious application for it that some other drug could not meet, some other single compound could not meet.

Chairman

315. Should it be cannabis or individual cannabinoids which should be given to patients?

A. There is a certain amount of debate going on at the moment amongst scientists and doctors and others as to whether it should be cannabis which is used as a medicine or whether single chemicals should be used, drugs like THC or nabilone. My own view is we do not know the answer to that. My Lord, you touched on this earlier when you said that some patients claim that cannabis is superior to drugs like nabilone, those are the anecdotal claims. The problem is there are various possible explanations for that. One is that you are comparing smoked cannabis with oral THC and nabilone. I have already said that oral THC, nabilone, is a problem because of the varied absorption and so on, it is not the ideal route, whereas smoking is a very good route apart from the harm the tars in the smoke may do. Another possibility however, and an interesting one, is that cannabis may be superior because some of the constituents of cannabis which themselves do not interact with the receptor may fine tune the effect of

the active constituent. There is some animal data to support that. There are two constituents in particular: one is cannabidiol which does not interact with the receptor but is a very potent inhibitor of drug metabolism, the P450 system of enzymes. It has been shown that it can alter the intensity of the effect produced by THC in animal studies. Another one, cannabinol can also modulate the effects of THC. Some effects go up, some effects go down in intensity, it depends on the effect you are studying. This is in animal studies. The bottom line then is that it is possible there may be some constituents of cannabis which are important because they modulate and fine tune the effect of the active constituent, perhaps to therapeutic advantage. That remains to be demonstrated. I think that what is really needed is a clinical study which compares a single chemical with cannabis, that is what you need at the end of the day to establish which is better. The only way you can do that is to have a proper clinical study.

316. [Unallocated]

Lord Rea

317. I am fairly sure you would agree with the statement that there has been too little clinical research done on cannabis and cannabinoids particularly with regard to MS. If that is the case whose job would you say it was to fill the gap? Could you explain the initiatives being taken by your research society, the International Cannabinoid Research Society, and the Royal Pharmaceutical Society to fill the gap? Have you personally been involved in trying to move this along?

A. I think the main problem is that drug companies have not stepped in, particularly on the agonist side, they have stepped in on the antagonist side, there are blocking drugs available already, which we have discussed, but they have not stepped in on the agonist side, the CB1 agonist side, the side which might help with disorders like multiple sclerosis, with spasticity and pain. Why they have not done this, I do not know. One possibility is that they are worried about the psychotropic effects of these drugs and have been unable to separate those out, as we discussed earlier. They might also be worried by the fact that cannabis is pretty well available in this country now and why should they develop a very expensive drug when someone can go down the road and get cannabis for a relatively small amount of money. At the end of the day if they do not step in who else will? Another barrier to clinical research, I think probably has been the fact that cannabis is used recreationally which means that some people do not take these drugs seriously as potential medicines because they focus on the recreational use. I think it is very important that one should separate out the medical and recreational uses of these drugs. When one is looking at the medical issues you realise that these drugs do have adverse effects but so do all drugs and at the end of the day we are interested in the ratio of the benefits to the risks. We should treat these drugs as we would any other potential medicine in coming to conclusions about their usefulness. Funding I suppose is another problem because if drug companies do not fund this kind of research,



12 May 1998]

DR ROGER PERTWEE

[Continued]

Lord Rea *contd.*]

and clinical research is very expensive, then who is going to fund it? My hope is perhaps that an influential group such as this Committee in fact might be able to play some part by perhaps liaising with the Department of Health to ensure as far as this Committee can that clinical studies definitely do go ahead and that they are funded as soon as possible. I think it is in everybody's interest to gather objective conclusive data—clinical data—about the therapeutic potential cannabinoids as soon as possible. We are not in a situation where these drugs are not being used at the moment, cannabis is already being used, albeit illegally, by people with MS and spinal injury and so on. We are not in a situation where we can wait and see. I think it is very unsatisfactory that people are self-medicating with cannabis because of its adverse effects. I would much rather see them taking cannabinoids under medical supervision. I think it is very important that a clinical study is started as soon as possible. You also asked about the Royal Pharmaceutical Society initiative. There are in fact two clinical groups in this country. The first one we set up last summer, it is what we call the Clinical Cannabinoid Group. That was set up after a one-day meeting that was held at the Royal Pharmaceutical Society on the therapeutic potential of cannabinoids. This group is very informal, it is a forum really. We do not meet, we are not funded so we cannot afford to meet because I am in Aberdeen and other members are in Southampton, for example, but we can exchange ideas by E-mail, that is not a problem. We are all people in this group who are very keen to see clinical trials set up and who would like to be directly involved in these clinical trials. This is a group which can exchange ideas and pool expertise. That is one group. Perhaps more importantly a second group has just been set up which has not got a name yet, it is so new, but I will call it for the sake of clarity the Clinical Cannabinoid Working Group to distinguish it from the other one. This was set up by Professor Moffat of the Royal Pharmaceutical Society and myself. It is much more formal than the other group. Its aims really are to set up guidelines for clinical trials with cannabinoids and to do everything possible to get trials under way. The sort of people who are members of this group, apart from myself and Professor Moffat, are Dr Clements of the Royal Pharmaceutical Society, we also have senior representatives of the National Health Executive, Medical Research Council and the MS Society as members on the group. It is going to be chaired I believe by Sir William Asher who I understand is a past chairman of the Committee on the Safety of Medicines so we will be in very good hands. Our first meeting will be next month and I am very hopeful that something may come of it. At the end of the day, however, it is another group talking about clinical trials. Really it is time to move forward from there to where actual clinical trials are set up. Going back to barriers, the most important problem has been the lack of a clinician who is prepared actually to mount a clinical trial. What we need is a clinician who has got the time and the motivation and the appropriate expertise to mount such a trial. I think the exercise should be led by a clinician if we are to get anywhere. As far as MS is concerned, another problem is the lack of conclusive end

measures for symptoms like spasticity. This is very difficult to measure, you get subjective information but it is very difficult to measure objectively. If you are going to do a cannabinoid trial you want to come out with some conclusive data. If your end measure is not very good you are not going to do that. We really need to decide if there is a good end measure for spasticity or maybe move on to something like pain which might be easier, although again that is subjective. The other problem really, which I will end on, is we need—as I mentioned already—better formulations and modes of administration. We should be working on that in parallel, I would have thought, with setting up clinical trials. You might argue we need the formulations before we do the trials but that could take forever so I think we should get on with the trials anyway.

Lord Porter of Luddenham

318. [Unallocated]

319. [Unallocated]

320. What would be the mechanism for setting this up?

A. Perhaps the best way forward is for the Department of Health to call for someone to mount a trial.

321. That would be?

A. For the Department of Health to call for tenders or whatever for a clinical study to be set up and to ring fence some funding for that.

Lord Butterfield

322. Presumably it would work with the Medicines Control Agency.

A. Yes.

323. Marijuana contains 488 substances; that includes 66 cannabinoids. If we are going to do any of these trials it may be that we are going to have to ask people who self-medicate who may come in to provide us with samples of their particular cannabis, so we can have those broken up and chromatographed or whatever you do to find out what the differences are. If there is a difference between the mixtures of all these compounds, 66-plus, it is going to be not unimportant as the research goes on to have base line core information somewhere, that you can turn back to see whether something that comes up unexpectedly can be explained by what those people are actually using. As you get on with your trials, it might not be a bad idea to keep some of the material they are using on the side, as people do with epidemiological studies, they put stuff in the deepfreeze and call on the serum for analysis later as necessary.

A. Yes, that is a very good point. It is perhaps also worth mentioning that these days I believe it is possible to grow strains of cannabis which have very reproducible levels, certainly of the standard cannabinoids. So you can, I think, come up with a standard preparation these days.



*12 May 1998]*

DR ROGER PERTWEE

*[Continued]**Chairman*

324. Is one of the problems that you have rather soft end points? We are dealing with substances which would relieve symptoms rather than actually prevent death. You have to devise instruments to measure the symptom relief and that may actually be another reason for the urgency not being quite so great because it is not a life and death issue, it is more helping people to feel more comfortable.

A. That is right. Of course, patients do feel extremely uncomfortable, this is the problem. The pain from the muscle spasm can be excruciating. I had sciatica once, and that was extremely painful. In a way I am glad I had it because it made me realise how much pain can be involved in muscle spasm.

*Lord Porter of Luddenham*

325. We have been told that THC is really the predominant cannabinoid in marijuana. Do the others do anything much at all? Are there any tests which compare gram for gram the effect of THC and THC in marijuana? In other words, does the other stuff make any difference?

A. There were some studies done well before the discovery of receptors, we are talking about 20 years ago, which demonstrated that some of the other constituents do modulate the effects of THC. It was not a comparison between THC and cannabis but between the THC and THC in the presence of, say, cannabinal and cannabidiol, which are two of the other plant cannabinoids. Certainly there was evidence for interaction. These others cannabinoids did seem to alter the intensity of the effects produced by THC, sometimes enhancing effects, sometimes having the opposite effect. I think that is worth looking at again.

326. I am terrified about the prospect of having to do chromatographs for them all and then test them. One must have a means of limiting it.

A. I think you can narrow it down. There is no good reason for saying this but you might want to narrow it down just to the cannabinoids, dealing with 60-odd compounds but that is still quite a lot. We would expect there to be hundreds and hundreds of compounds in a plant. I suppose the other way is to

start with THC and then gradually add in other compounds and stop when you have got a good drug. It does not matter if you are mimicking cannabis or not, all you want is a good drug. I suppose that might be the easier way around that.

327. Do you have any inkling how different in its effects is THC pure and THC in marijuana in the same amounts?

A. By itself or when it is present with the other material?

328. You are administer cannabis with a certain number of grams to THC and comparing that with a certain number of grams of pure THC.

A. That is a very interesting point. You could do a relative potency study, for example, and express the potency in terms of THC, that is what you are saying, and look for a difference in potency or the maximum or whatever. I do not think that has ever been done, at least I am not aware of it. If that has been done it would be very interesting.

329. It surprises me that it has not been done.

A. It may have been.

330. It seems the first experiment that one would do on cannabis.

A. It may be I have done it but it was such a long time ago that I have forgotten it. When we first started working on cannabinoids we were in fact working with cannabis, National Health Service cannabis I may add because we got it from the NHS supplier.

*Lord Butterfield*

331. The anecdotal evidence that has been put to us suggests very strongly that there is a difference.

A. The problem is there is also the route of administration difference.

*Chairman*

332. Dr Pertwee, thank you very much.

A. Thank you very much, my Lord Chairman, it has been a pleasure.

---

TUESDAY 9 JUNE 1998

---

## Present:

Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.  
Perry of Walton, L.  
(Chairman)

Porter of Luddenham, L.  
Rea, L.  
Soulsby of Swaffham Prior, L.  
Walton of Detchant, L.  
Winston, L.

---

**Memorandum by the Multiple Sclerosis Society**

## CONTENTS

Introduction  
Context of MS  
Assessing The Evidence  
Anecdotal Evidence  
Trial Evidence  
Constructing An MS Cannabis Trial  
Conclusion

## INTRODUCTION

1.1 The evidence submitted by the Multiple Sclerosis (MS) Society focuses solely on the issue of the medicinal impact of cannabis use. The MS Society believes that the question of the therapeutic effects of cannabis should be judged according to the same criteria which apply to the assessment of any proposal for a new drug therapy. The current licensing system for new drugs demand that therapies meet standards for quality, safety and efficacy. The Society believes that there is currently insufficient evidence to assess whether cannabinoids meet these three requirements. Just as we argue that the trial evidence for the efficacy of new beta interferon treatments is sufficiently strong to justify their prescription, in the absence of comparative evidence for cannabis we cannot support its use in clinical practice.

1.2 Below we give our assessment of both the anecdotal and the medical trial evidence about the use of cannabis as a treatment for multiple sclerosis. The Society believes that the evidence about the therapeutic effects of cannabis is so limited that it is essential that further research is undertaken.

## CONTEXT

2.1 It is important to consider why discussions about the therapeutic effects of cannabinoids for MS are taking place. The persistence of medical debates about the medicinal uses of cannabis reflects a concern within the medical profession and amongst many patients at the lack of effective symptom control treatments for MS.

2.2 MS is the most common disabling neurological disease of young adults, with an estimated 85,000 living with the condition in the UK. Most people are diagnosed with MS in their early adulthood and therefore are faced with living with MS for many decades.

2.3 MS is an extremely variable disease but it often manifests itself with symptoms of spasticity, pain and bladder and bowel dysfunction. The MS Society *Symptom Survey* of people with MS showed that 74 per cent of respondents experienced spasticity, with 51 per cent experiencing muscle spasms and 54 per cent citing pain as a symptom. MS is also a life long illness and therefore unpleasant symptoms may persist for a very long period.

All MS treatments therefore have to be evaluated to assess whether they will be of long term use.

2.4 Currently, there are very limited treatment options which people with MS can use for symptom management. This is especially true of pain control, where few treatments are effective. It is a reflection of the lack of attention paid to proper management of spasticity and associated symptoms in MS, that tizanidine (zanaflex) licensed in late 1997, is the first new drug to receive an authorisation for treating neurological spasticity in 20 years. Severe tremor can be debilitating in MS and although baclofen and diazepam are used, severe cases may require surgical intervention (thalamotomy or thalamic stimulation).



9 June 1998]

[Continued

2.5 Available treatments for spasticity are baclofen, dantrolene, diazepam and recently tizandine. These afford partial relief and can have unpleasant side-effects. Nevertheless the MS Society Symptom Survey showed that 37 per cent of people with MS in an MS Society surveyed were receiving baclofen.

2.6 Incontinence is one of the most common symptoms of MS (66 per cent of people with MS have bladder and bowel problems) and incontinence was rated as the second most common symptom causing distress for those living with MS. Drug treatment with oxybutinin and desmopressin is available, but in the MS Society Symptom Survey only 15 per cent had been treated with oxybutinin.

In the variable range of patterns which multiple sclerosis takes, most people will initially experience relapses, or attacks, followed by periods of remission. Most people in this group will continue in employment. The issues around employment and operating machinery whilst on medication do not apply to all individuals with MS, however, as 10 per cent experience progressive MS, which may progress rapidly and about 50 per cent of those whose multiple sclerosis began in a relapsing-remitting form, will progress over time to a point when they are no longer able to work. Individuals whose MS has developed to a point may experience pain, spasticity, tremor and extreme fatigue exacerbated by sleepless nights caused by spasms and nocturia.

2.7 This situation presents an urgent need for more effective symptom control therapies in MS. Could cannabis or one of its derivatives be an effective MS treatment? Some people have turned to cannabis in despair at the ineffectiveness of existing licensed therapies. Some individuals have reported that cannabis is helpful in ameliorating some of the symptoms identified above.

2.8 Cannabis is reported as helping with:

- muscle spasms;
- muscle stiffness;
- tremor;
- pain;
- incontinence;
- sleep (24 per cent of people with MS say that their illness has a major impact on the quality of sleep).

*To assess the benefits of a treatment a number of issues need to be addressed:*

- effectiveness;
- safety, in terms of the risk/benefit ratio involved, do the benefits substantially outweigh any identifiable side effects.

both in the short and long term

#### ASSESSING THE EVIDENCE

3.1 Anecdotal accounts from individual people with MS have extolled the ameliorative virtues of cannabis. However little attention has been given those who have reported negative effects. The MS Society invited individuals with MS who had tried cannabis to relay their experiences. We have summarised the results of this exercise below. The survey showed a more mixed picture than is generally assumed.

3.2 Only six medical trials have been undertaken to test whether cannabis is efficacious in MS. The Society's assessment of these trials is outlined in the section below. In addition little work has been done on evaluating whether a particular combination of the constituents of cannabis—cannabinoids, will have greater efficacy as an MS treatment.

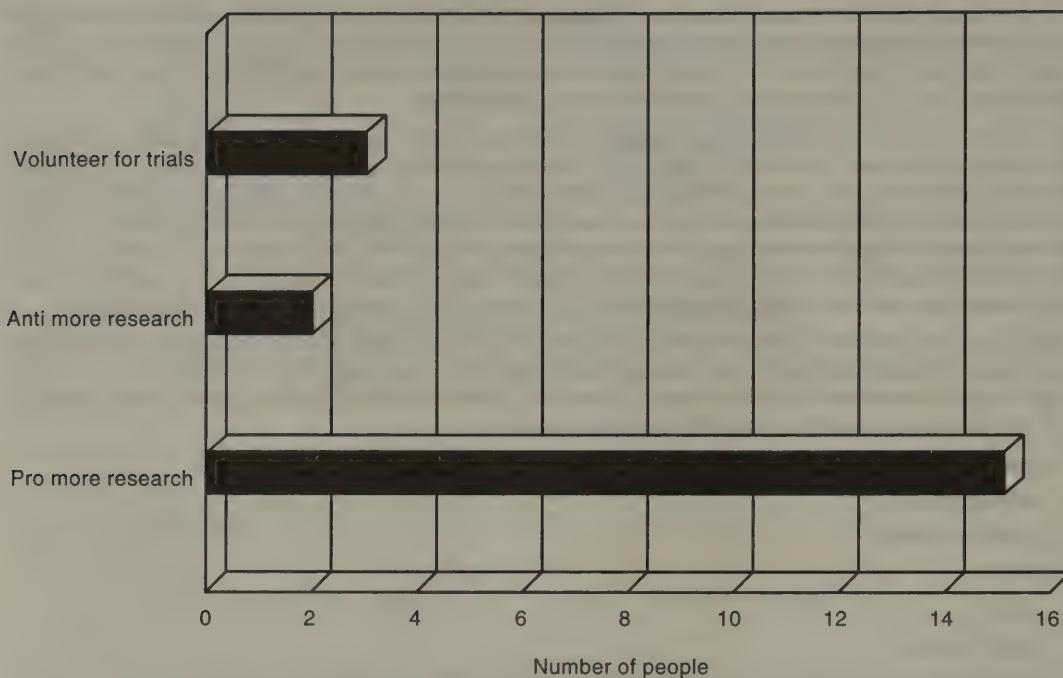
#### *Anecdotal Evidence On Cannabis Usage In Multiple Sclerosis*

4.1 In the November/December 1997 issue of the MS Society's magazine, *MS Matters*, a request was made for anyone who wanted to express a view on research into the use of cannabis in MS to write to the Society.

4.2 A total of 48 letters were received in response to the request, giving views on research and personal experiences. Of those who indicated a preference, most were in favour of further research into the therapeutic usage of cannabis.

9 June 1998]

[Continued

**Views on research into MS and cannabis**

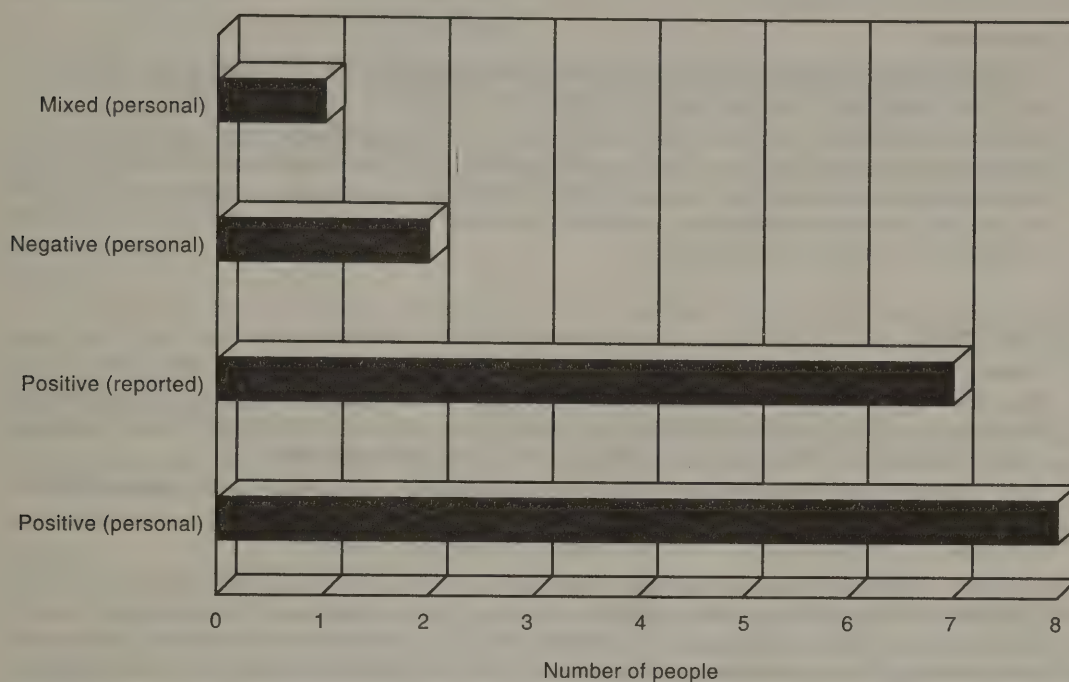
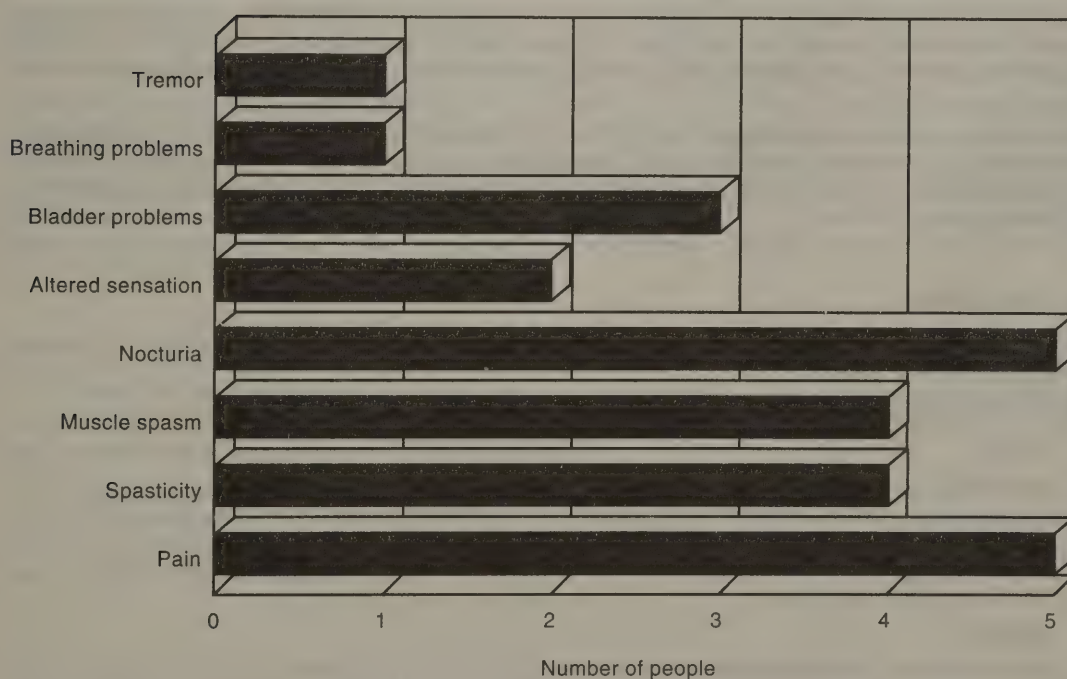
4.3 Of the 48 correspondents, 20 called for cannabis to be made available on prescription, but eight of these were also in favour of more research. Two correspondents expressed concern that it would be difficult to restrict cannabis to the therapeutic purpose for which it was intended if prescribed.

4.4 Fifteen correspondents gave details of positive personal experiences of the use of cannabis, eight as personal experience and seven reported accounts. There were also two reports of negative and one mixed experience. These experiences are tabled below, with details of the symptoms reportedly relieved by taking cannabis.



9 June 1998]

[Continued

**Experiences of using cannabis for MS****MS symptoms reportedly relieved by cannabis**

9 June 1998]

[Continued

4.5 The following are examples of positive and negative personal experiences of the use of cannabis to relieve multiple sclerosis symptoms:

*Positive experiences:*

"I often smoke it at night when muscle spasms prevent sleep and for this use it is very effective. It also has a lesser, but noticeable effect on improving sensation."

"Over a month ago, I did have the opportunity to try cannabis—the first time ever. . . I felt rejuvenated in my right leg and found I could walk more easily and climb stairs as I had done years ago when my walking was fine. I was also able to carry a full cup of tea without spilling it. I believe the benefits I experienced were that it reduced and almost seemed to remove the spasticity. I could not believe it. It felt I had a new leg."

*Negative experiences:*

"I have smoked cannabis resin this year. It did not relieve my MS condition. Neither did it relieve the pain. However, I was aware of sensations that are similar to the effects derived from drinking alcohol. A possible side effect that I suffered from was a temporary weakening of bladder control. I was disappointed. This made me wonder whether I had 'missed the point'."

"My initial reaction to it was very positive. I was convinced that it reduced the pain and greatly improved my ability to walk. However, after having taken it for at least 4 months and possibly 6, I thought the beneficial effects were less marked, so I stopped taking it."

4.6 The number of letters received in response to the query in *MS Matters* was small, but re-inforces the anecdotal information received by the Society's information and Helpline services. The majority of people who try cannabis report beneficial effects, but a significant minority report either no effect, an effect which wears off over time or adverse reactions such as balance problems, bladder weakness and concentration problems. People with MS also express concern about the effect of smoking cannabis on their general health.

4.7 This anecdotal evidence contains findings which accord with other surveys of MS cannabis users. However evidence of this nature cannot, of itself, be regarded as conclusive. One factor which must be taken into account when interpreting this type of evidence is whether there is an inherent bias present in these type of surveys. It may well be the case that individuals with more positive experiences are more likely to respond to these surveys because of the incentive which exists to promote their experiences given the legal status of the drug.

4.8 Irrespective of these considerations, the MS Society believes that evidence of the drug's effectiveness has to be judged against more rigorous standards. Meeting these standards requires that properly controlled medical trials take place. The value of the anecdotal reports is that they are able to inform the areas such trials would investigate.

*Existing Trial Evidence*

5.1 There have been six controlled clinical trials published in MS, four of them used oral cannabinoids; in two trials, cannabis was smoked.

Positive effects were reported in relation to the following symptoms:

- tremor;
- spasticity;
- spasms;
- nocturia.

Negative effects were reported on:

- balance.

5.2 However these trials were very small scale. The scale of the trials is a particular problem in the context of this illness. MS for many people is a fluctuating illness. MS is also very varied in its effects with a multiplicity of symptoms. The variability of the illness means that the outcomes of small scale trials cannot hope to be representative of how many people with MS would respond to treatment with cannabis.

**HOW AN MS CANNABIS TRIAL SHOULD BE CONSTRUCTED**

6.1 Constructing a controlled medical trial to evaluate the effectiveness of cannabis as an MS therapy would not be a straightforward exercise. The MS Society believes that any trial has to take into account the following considerations:



---

9 June 1998][Continued

---

### *Trial Design*

6.2 The “gold standard” for a trial is a multi-centre, double blind, placebo-controlled, crossover trial, with one variable which can be objectively and reliably measured. Given the variability of the illness as outlined above, a large trial of long duration is necessary.

6.3 There is an additional difficulty in constructing a placebo-controlled cannabis/MS trial. Given the psychoactive effects of some cannabinoids it could be difficult to “blind” the participants in a trial.

This reinforces the need for an objective outcome measure to be chosen which will minimise the effects of any bias. However the difficulty of blinding trials remains a significant handicap in designing a clinical trial for this drug.

### *Outcome Measures*

6.4 Reliable and objective measurement of physical symptoms may be problematical with many of the symptoms experienced by people with MS. In some instances it would be difficult to verify whether or not a patient was or was not experiencing a symptom.

6.5 Nonetheless, there are many measurements/scales available. Quality of life measurements are particularly relevant to research on this subject. There are quality of life measures, such as MSQUOL, which are specific to MS. The 1998 Health Technology Assessment report on beta interferon therapies shows how MSQUOL can be effectively used to identify the impact of MS on the health of individuals.

### *Which Symptom Should Be Tracked?*

6.6 It is difficult to choose one symptom given the multiplicity of symptoms present in MS. This is where information from anecdotal reports is essential. Anecdotal findings can inform the choice about which symptoms to track during trials. There is also a “public interest” need to investigate symptoms which are least responsive to existing treatments. Equally, there is a need to focus on symptoms, where although an effective treatment exists, a large number of individuals do not respond to this treatment.

### *Choice of Treatment*

6.7 While a single cannabinoid which can be produced to a consistent standard may seem attractive; with at least 66 cannabinoids to choose from this may be impractical. In addition, there may be many individual cannabinoids which are beneficial, with a possibility that an interplay between cannabinoids which produces a beneficial effect. Trials could take place in two phases. The first phase could consist of a trial of whole cannabis, with an active placebo to mimic the psychotropic effects of cannabis, in order to overcome the problem of blinding. This would allow some results to become available at a reasonably early stage. The next phase could consist of trials of specific compounds of cannabinoids. Specific cannabinoid compounds which do not have psychotropic effects could be identified.

### *Safety*

6.8 While no drug treatment is absolutely free of side effects, it is important in a long term chronic condition that both long and short term side effects are monitored. At present the existence or scale of the drug's side effects among MS users are largely unknown.

6.9 It is particularly important that any treatment for MS does not make other symptoms of MS worse. Given the health risks of smoking cannabis other methods of administration should be considered. Ultimately, medical research has to establish the balance between any clinical benefits of the drug and the scale of identifiable side-effects.

### *Cost*

6.10 There is little support from the pharmaceutical industry for cannabis trials due to financial disincentives. Clinical trials are expensive and whilst the MS Society is willing to support a well designed trial with limited funds at our disposal and other research commitments, partners may have to be sought.

### *The Way Forward*

6.11 In order to clarify these issues, the MS Society with the Royal Pharmaceutical Society are facilitating a working group of experts on cannabinoid research along with interested clinicians and neurologists to determine the most best and most practical approach to clinical trials of this drug.

9 June 1998]

[Continued]

## CONCLUSION

7.1 The MS Society believes that there is an urgent need for new symptom control therapies. However any proposal for therapy has to conform to stringent medical standards. These standards must entail rigorous and well constructed scientific trials.

7.2 The Society supports the view of the BMA that controlled trials of cannabinoids should take place for patients with spastic disorders which have not responded to other drug treatments. We believe that these trials have to take into account the considerations raised in this paper. *Unless and until such trials are undertaken and a therapeutic benefit is demonstrated, the MS Society would not support the prescription of cannabis for people with MS.*

7.3 There remains the question of people with MS who are already using cannabis as a treatment for their illness and how they should be treated within the criminal justice system. The press has recently highlighted cases of a number of individuals in this situation.

7.4 The MS Society does not encourage people with MS to break the law. We do however understand why some people who face intolerable symptoms have chosen to make their own decision about cannabis use, recognizing the implications of their choice. Where the medical evidence warrants it, we hope that the police and the courts would deal with such people in an appropriately compassionate fashion.

*Dr Lorna Layward*

*Ruth Carlyle*

*Dr Matthew Sowemimo*

## Examination of Witnesses

DR LORNA LAYWARD, Research Manager, and MRS RUTH CARLYLE, Manager of Information and Education, Multiple Sclerosis Society, were called in and examined.

*Chairman*

333. Good morning and thank you very much for coming. Would you like to begin by introducing yourselves and telling us briefly something about the Multiple Sclerosis Society and its activities?

(*Mrs Carlyle*) Thank you, Lord Perry. My name is Ruth Carlyle and I am the manager of information and education for the Multiple Sclerosis Society. I manage the Society's information services and I look after the professional education programme for health and social care professionals. I actually qualified originally as an information scientist and as a medical librarian. My interest prior to working with the Multiple Sclerosis Society was with the Motor Neurone Disease Association, training originally with the pharmaceutical sector. I am very glad to have the opportunity to be able to represent the MS Society to the Committee. My colleague will introduce herself.

(*Dr Layward*) My name is Lorna Layward. I am the research liaison officer at the MS Society. I look after the Society's research programme. We are the major funder of medical research into MS in the United Kingdom. I also interpret science and research for the MS community. I have a PhD in immunology. I am not medically qualified. Previous to this appointment with the MS Society, I worked for many years as a bench researcher into diseases that either had a immunological aetiology or pathogenesis. The Society is the largest charity supporting people with MS in the United Kingdom. We have 55,000 members and 35,000 of them are people living with MS. The Society has twin aims. One is to support people with MS, their families and their carers in their day to day needs, securing the care that they need. The other aim is to support research into the treatment and the causes of MS. Our work includes raising awareness of MS, of living with MS and the need for research into the condition.

We also provide services for people with MS, such as support through our help line and information. We provide respite care and financial assistance at both a national and a local level. We provide information for people with MS and health professionals about the disease and about health care treatments. As I have said before, we fund a large amount of research. We are the major funder. We have about £10 million committed to medical research at the moment. Some of our research does go into looking at symptom control. We also are a campaigning Society. We campaign on behalf of people with MS, on all aspects of living with the condition. That is a sort of general overview of what the MS Society does. Specifically about the therapeutic applications of cannabis in MS, we wish to say that we approach this question in the same way as we would any other proposal for any other treatment for MS. That is, we need to establish clear, objective, scientific evidence of benefit before we can recommend that the drug can be used. Putting it in context, there are many people with MS who have very distressing symptoms for which there is either no effective treatment or the existing treatments are unsatisfactory. There is also a body of anecdotal evidence that cannabis can alleviate some of the symptoms of MS and a small number of clinical trials that have shown some benefit of cannabis or cannabinoids. Given that there is a need for better symptom control in MS and that there is existing evidence of the potential efficacy of cannabis, it is timely that we establish larger rigorous clinical trials to determine the efficacy and safety of cannabis or cannabinoids in MS.

334. What are the particular symptoms of MS that patients complain most frequently about?

(*Mrs Carlyle*) In relation to the symptoms, I must emphasise that multiple sclerosis is an extremely variable condition. There are predominantly three main patterns that people experience: one of these,



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Chairman *contd.*]

relapsing and remitting, the most common, involves the attacks of symptoms coming on and then periods when there is a remission with perhaps full symptom loss or just partial, residual symptoms remaining; other individuals will experience a progressive condition. Within that context, the symptoms that people complain about vary very dramatically. We encouraged a study in which we were involved directly ourselves in which we asked people which symptoms caused them most distress by identifying first of all which symptoms they most frequently experienced. We found that, in terms of the most frequently experienced symptoms, fatigue came out as most frequent with 95 per cent of people across the very broad forms of multiple sclerosis experiencing fatigue, which can sometimes be extremely disabling for individuals. About 84 per cent of people experience balance problems. Problems with muscle weakness were experienced by 81 per cent of people. Taking selective examples, muscle spasms were experienced by 66 per cent of people, so still a very high proportion of people, given the variability of multiple sclerosis. Pain was experienced by 63 per cent of people. Incontinence was experienced by 76 per cent of individuals and tremor by a significant 35 per cent of people with MS. Again, tremor can be extremely disabling. Looking then at the symptoms which people complained about in terms of experiencing most difficulty or distress as a result of those symptoms, again fatigue came out most highly with 65 per cent of people citing fatigue as being one of their top three symptoms causing distress. Bladder and bowel problems: 50 per cent of people were caused distress. Muscle weakness: 44 per cent of individuals. Pain: 18 per cent and tremor: six per cent. Although the numbers are very low, some of the symptoms in relation to tremor particularly can be very disabling. The survey itself reflects the concerns which people with MS express to the Helpline and our other information services as well as within this particular symptom survey.

335. In what respects do you regard the current licensed treatments for MS as inadequate?

(Mrs Carlyle) The inadequacy lies in the fact that, for many people, with the variability of multiple sclerosis, there is still an increased uncertainty with the variability of how well their symptoms can be managed. I am not a medic myself but I will cite some of the main examples of symptom treatments which people currently receive for multiple sclerosis. In relation to the severe tremor which I mentioned as being extremely disabling, as it can prevent people from being able to feed themselves and it prevents them from being able to dress themselves and makes them totally dependent, baclofen and diazepam may be used with limited effectiveness. One of the other options is invasive surgery such as thalamotomy or thalamic stimulation which can be, in extreme cases, effective but often for short periods of time and the surgery being extremely invasive is distressing in itself. In relation to spasticity—which I mentioned, 74 people experience spasticity in some form—the loss of muscle tone resulting in stiffness or spasms is often treated by baclofen, diazepam and tizandine, none of which again is very effective. In some instances, one of the more severe side effects can

actually be muscle weakness. An individual who might have been able to transfer from their wheelchair to their bed using their own spasticity to keep them stiff, once they have muscle weakness, is no longer able to transfer himself and he becomes dependent on other people. With fatigue, that most disabling aspect of MS, 65 per cent of people in our study cited fatigue as being one of their top three distressing symptoms. That has very, very limited drug assistance. At this point in time, most people's fatigue is managed by restricting their lifestyles, choosing not to do two particular activities on one day. For example, not doing the ironing on the same day as the shopping. There is some drug assistance such as amantidine but, in our symptoms survey, only five per cent of people with MS were actually offered amantidine to help them with their symptom control in relation to fatigue. The last example I would like to cite is in relation to incontinence which includes nocturia, people's inability to go through the night without having to pass water. It is a restricting and embarrassing condition. There is a very limited use of oxybutinin. About 15 per cent of people with MS use it or desmopressin. Most management is based around diet, fluid intake and catheterisation, so again it is practical management rather than drug management. If it is not managed properly, then many people experience problems with urinary tract infection and other serious complications. At this point, my Lord Chairman, I would like to emphasise that there is a variability in relation to the availability and effectiveness of the current drug treatments for multiple sclerosis.

336. We have been told that cannabis works in only a proportion of the patients who have tried it. Is it not true that all the synthetic chemicals that are used only work in a proportion of patients as well?

(Mrs Carlyle) It is indeed true. The only difference in relation to licensed drugs is that we have some sense of what the side effects will be and who the ideal candidates will be for taking particular drugs. With an unlicensed drug, obviously we do not have the clinical evidence to help us, to use as a benchmark for people to make a choice in their symptom treatment.

337. Has anandamide been tested at all in the treatment of MS?

(Dr Layward) Are we talking about anandamide, the endogenous cannabinoid?

338. Yes.

(Dr Layward) The endogenous cannabinoid, as far as I know, has not been tested. I really cannot say without doing a search and finding out.

*Lord Walton of Detchant*

339. Of course, there is indeed evidence, is there not, that beta interferon and alpha interferon may have a beneficial effect not only for relapsing and remitting MS but now evidence is emerging about its beneficial effect in even the chronic progressive form. At one point you mentioned thalamotomy for tremor which can be so disabling. The side effect of that which is most disturbing is intellectual impairment, which is almost invariably a consequence of a bilateral procedure. I think it is for



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Lord Walton of Detchant *contd.*]

that reason that it is used so little. Are you aware of any physiological evidence which supports the alleged beneficial effect of cannabis on bladder control?

(*Mrs Carlyle*) At this point, we do not know what sort of numbers can benefit. In terms of anecdotal reports from individuals, many individuals report that it stops nocturia particularly and their feeling is that bladder control, not necessarily bowel control, is improved by the taking of cannabis. At this point it is purely anecdotal evidence and we have no means of quantifying it.

340. There is nothing to indicate at the moment any understanding of the basic scientific mechanism through which it acts in that situation?

(*Dr Layward*) No, not that we are aware of.

341. Could you try and give us an estimate of the proportion of MS sufferers who are currently making illegal use of cannabis for relief of symptoms? Can you tell us what is the attitude of their doctors? If found out, would you like them to be treated by the law, as you have suggested, in an appropriately compassionate fashion? Have you any information about what has happened in typical cases?

(*Mrs Carlyle*) Estimates vary in relation to the number of people who are currently taking cannabis because of the obvious legal issues. In our symptoms survey, we did ask people whether they were using cannabis to help relieve their symptoms and one per cent acknowledged that they had done so. It is probably higher than that. A large United Kingdom neurological centre estimated three to four per cent of their patients were taking cannabis for therapeutic purposes. In relation to the attitude of doctors, attitudes clearly vary according to context. In a hospital situation where a hospital doctor feels he has personal liability for allowing somebody to break the law on his premises, they are obviously less likely to either condone or appear to condone the use of cannabis than a general practitioner. In relation to the viewpoints expressed by people with multiple sclerosis to the Society on what their doctors are saying to them, most state that their doctors are mildly supportive of what they are doing. The Society itself, whilst understanding the urgent need for better symptom management, does not actually condone or encourage individuals in breaking the law. On the third part of your question, in relation to the compassionate fashion in which we ask for people to be treated: in the reported cases of which we are aware, the typical response is that people have tended to be let off with a suspended sentence, where it is proven that they are people with MS using cannabis for therapeutic purposes, as opposed to recreational purposes. Some of our otherwise law abiding members express concern about the stress of going through the standard criminal justice system. In many ways, our reference to a compassionate fashion is the manner in which people are handled by the criminal justice system as much as the final verdict.

342. Have you been aware of anyone with MS who has been convicted for smoking cannabis?

(*Mrs Carlyle*) In relation to reports, we have very little evidence at this point. We have third party

reports which are very difficult to evaluate at this stage.

343. But no firm evidence?

(*Mrs Carlyle*) No firm evidence, no.

344. My last point arises out of your comments on fatigue which is a very common feature. It sometimes responds to antidepressant agents because depression is also an extremely common complication of multiple sclerosis. Is there any evidence to suggest that people are using cannabis for the treatment solely of fatigue?

(*Mrs Carlyle*) It is very difficult to assess exactly how people are using cannabis at a point when we have anecdotal evidence and people are citing several different symptoms, often simultaneously. Yes, you are quite right in relation to the use of tricyclic antidepressants for the management of fatigue.

Lord Nathan

345. Relating to the prosecutions, can you give any indication as to the number of which you are aware—of course, it is in the public domain—and which courts, both geographically and by status of the court, the matter comes before?

(*Mrs Carlyle*) I regret I would not be able to answer the question without further investigation but we would be happy to come back to you in relation to the question.<sup>1</sup>

Lord Dixon-Smith

346. Could you comment, please, on the evidence which we have received from Clare Hodges, Geoff Vincent, Diane Lewis and Ms Brown? Is their tale a typical tale or is it an extraordinary one?

(*Mrs Carlyle*) I think that the evidence presented is typical of the very positive examples of anecdotal evidence that we receive from individuals. Also, I think that the assessment that Clare Hodges produces within her evidence of the fact that there are some people with no or negative effects is typical of some of the experiences that we have had. We feel that the anecdotal reports are very informative and very moving but do not of themselves constitute scientific evidence. We feel that the key value of this data as presented is that it will inform further enquiry.

347. I think you said one per cent of your 35,000 affected members are perhaps using cannabis, if my memory is correct. It is really quite a small proportion of the whole. Are there MS sufferers outside your Society who increase that number quite dramatically, or do you think that you have the whole spectrum of MS sufferers within your knowledge so that that is the scale of the problem that we are discussing?

(*Mrs Carlyle*) It is a very difficult issue in relation to numbers. As we mentioned in our introduction, 35,000 out of the approximately 85,000 people with MS in the United Kingdom are currently members of our organisation. How representative they are of the group at large is very difficult to tell without further

<sup>1</sup> See supplementary memorandum, p 100.



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Lord Dixon-Smith *contd.*]

study. Again, there are the problems of how many people will actually admit to taking cannabis in relation obviously to its current legal status. My honest answer is that we do not know and it would be very hard to find out the current status. There may well be people within other groups, other communities in the MS world—there are other MS organisations—where there may be a high proportion of people taking cannabis for therapeutic benefit.

Lord Kirkwood

348. When you have evidence of negative effects from people that you have cited, is there any evidence whether the negative effects are due to the mode of administration or the dosage?

(Mrs Carlyle) It is possible that it may be the mode of administration both in terms of route and in terms of dosage. At this point, it is impossible to tell on the basis of the anecdotal evidence but very often people will report severe adverse reactions after a first taking of cannabis and that may well be due to administration mode.

Lord Rea

349. I wonder if you could comment on the evidence of the neurologist, Dr Fred Schon? Can you answer his question about whether other MS sufferers with visual problems have been helped by cannabis? Also, the last question he puts in his evidence is: how can practising clinicians carry out even the simplest clinical studies on the effects of cannabis with the law as it is now, and should some way not be found of allowing clinicians to identify patients who claim cannabis to be beneficial, without legal risk to doctor or patient?

(Dr Layward) The evidence given by Dr Schon is a very interesting anecdotal report. We are unaware of any other reports about the use of cannabis with eye problems. This was an eye movement problem. In MS, visual problems are very common but that is due to many, many different things. In our studies, we estimate that 57 per cent of people with MS have had visual problems at some stage or other during their disease. The most severe one is optic neuritis which many patients present with. That is due to demyelination and inflammation of the optic nerve. It is often associated with a great deal of pain. There are other eye problems such as retinal vasculitis and problems with peripheral vision, blurred vision and double vision. It may be possible that cannabis can help with some of these visual problems. What we do not know is which one of the many different types of vision problems it could help. This is very interesting because it informs that this may well be something which could be looked at in clinical trials. We are only ever going to find out if we do proper, controlled, clinical trials. You asked specifically about his two questions. It does seem to be very difficult for a practising clinician to carry out quite simple clinical studies because of the legal situation of cannabis. Clinical trials can go ahead but it is difficult. Everyone has to get the right licensing, but the law does allow for clinical trials to go ahead. It

would be very difficult for a practising physician such as Dr Schon to have a look at just a few patients. In terms of informing people with MS, anecdotal reports are not really terribly helpful. What we need is to know, through proper, objective, controlled clinical trials, information as to whether cannabis is effective for the treatment of some of the symptoms of MS. We need proper clinical trials because we need to be able to inform people with MS whether it works or does not work. The second question was about allowing clinicians to identify patients who claim cannabis has been beneficial to their condition without legal risk to doctor or patient. I am not in a situation to be able to answer that question.

350. You would say that that is a question perhaps this Committee should consider?

(Dr Layward) Yes, absolutely.

351. I think the important thing about Dr Schon's example is that there is a patient who failed to respond to nabilone but did respond to something in the resin itself.

(Dr Layward) We have anecdotal evidence that, particularly in pain, some people are saying that cannabis works better than nabilone. There is certainly some evidence of that.

352. Can you tell us more about your views on the medical use of natural cannabis—that is, the actual plant product—as against such single cannabinoids as nabilone or dronabinol? How widely are nabilone and dronabinol currently used in MS and do you think they should be used more widely?

(Dr Layward) Natural whole plant cannabis is a substance that people are using at the moment. As I said earlier, we do have anecdotal evidence that nabilone may not be as effective for certain symptoms as cannabis. Given that there is a huge number of cannabinoids, over 60 cannabinoids, in cannabis it would be extremely time consuming and very costly to determine which cannabinoid or combinations of cannabinoids are effective in symptom control. Certainly in the first instance, that would be a time consuming and expensive exercise. Given the urgency of the need to establish whether cannabis is effective in light of the treatment failure for the many symptoms of MS, it seems prudent to first establish whether cannabis as a whole plant is effective in symptom control. It is possible to produce cannabis under controlled conditions, and to produce cannabis with known cannabinoid content. Should the efficacy of the whole plant be demonstrated in a proper, controlled clinical trial, it would then be logical to determine which cannabinoids or combination of cannabinoids are responsible for this effect and compare that with the whole plant.

353. Yes. How widely are nabilone and dronabinol used and are they used enough?

(Dr Layward) We know that dronabinol is rarely, if ever, used in the United Kingdom and we understand, if it is, it is on a named patient basis. Nabilone is occasionally used in the United Kingdom, we understand for symptoms such as spasticity and pain. However, when we asked what drugs people were using we found, in our survey of something like 250 people, that cannabis was used by

9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Lord Rea *contd.*]

one per cent but nabilone by only 0.03 per cent, so three times as many people were using cannabis than were using nabilone. It therefore seems that it is very infrequently used in MS.

Lord Dixon-Smith] If we know that dronabinol and the other extracted cannabinoid individually used is not effective, and we also know, if anecdotal evidence is to be believed, that the use of the whole plant with its 61 combinations is effective, what is the purpose of trying to refine the individual 61 into different combinations to try and find a particular combination which would actually work, bearing in mind that a variable combination of 61 component parts is an immensely complex system, because there are so many possible combinations both as to quantity of the individual variety and individual cannabinoids? Whilst it is a wonderful field of research which I think will go on probably for centuries before you have worked your way through the potential list, I just wonder why we need to push it that far? I can see one or two of my scientific friends looking at me slightly hesitantly.

Lord Porter of Luddenham] Not at all. I agree entirely and approvingly.

Lord Walton of Detchant

354. Is it possible that, by carrying out such research, it might be possible to identify an agent which is useful in improving spasticity, without having the psychoactive side effects?

(Dr Layward) Possibly, yes. In the first instance, we need to know whether cannabis is effective and what symptoms it is effective for. Then we have the problems of unwanted side effects. This would be a situation where it would be prudent to then try and dissect out what causes the unwanted side effects such as the psychoactive effects; and therefore home down on the cannabinoids that are of practical, symptom control use and try and remove the ones that we do not want and the side-effects we do not want.

Chairman

355. Has there ever been a drug used in the treatment of MS that does not have unwanted side effects?

(Dr Layward) I do not think there is any drug that does not have unwanted side effects. You are absolutely right. In terms of symptom control in MS, the drugs that are available all have significant side effects. I think it is naive to think that we can ever get a drug that is going to be completely side effect free.

Lord Dixon-Smith

356. Do we know that it is not the psychoactive effects which are relieving the cannabis symptoms?

(Dr Layward) May I answer that question and cite some unpublished research? One of the things that this whole question of reviewing the therapeutic potential of cannabis, particularly by this Committee, has done is raise a great deal of awareness. It has raised a great deal of awareness amongst basic scientists and we have facilitated some

research with an expert scientist who studies an animal model of MS. It is an animal model called EAE which is Experimental Autoimmune Encephalomyelitis. It induces an MS-like disease in mice, and they noticed that a number of the mice had a very severe tremor.

Lord Winston

357. Shiverer mice?

(Dr Layward) It is not the shiverer mice. This is immunologically induced EAE using myelin proteins. This disease is induced by an autoimmune mechanism. Some of these mice have tremors in their hindlegs and some in their forelegs. The experiment was to see whether cannabinoid receptor agonists can alleviate the symptoms. If you give them high doses, yes, there is a psychoactive effect. There is no doubt that the mice are behaving abnormally at high doses, but titrating the dose down you can see mice that have their tremor completely alleviated within one to two minutes of an IP injection of cannabinoid receptor agonists, but they are perfectly normal mice in the way that they are grooming themselves; they are wandering around and they do not appear to have any sort of psychoactive effects. Here we are starting to get basic scientific evidence for effective symptom control in an objective manner and this is something that is very new. A great deal of this sort of research has not in fact happened before. I must emphasise that these are preliminary and unpublished results.

Lord Rea

358. You cannot ask a mouse how happy it is feeling.

(Dr Layward) No, but you can observe the way that a mouse is behaving.

Lord Winston

359. On the point of the animal model, I know it is not a very good model for MS but has the shiverer been looked at to see about tremor?

(Dr Layward) That is an experiment that we were talking about doing with these people in fact, yes, to have a look at the shiverer mouse. Not to my knowledge has anyone looked at tremor control by cannabinoids in these animal models of demyelination and inflammation. This is the first time I am aware of this happening.

Lord Porter of Luddenham

360. Dr Layward, I am not very attracted by your policy of proceeding with research because, if one is going to get a result in any conceivably short enough time, you would surely do very much better looking at what we were really talking about, the comparison of nabilone and dronabinol with the natural plant, and you are surely going to get somewhere much more quickly, if you are going to get anywhere at all, with the single substances? You will never, surely, finish with a reproducible product in the first place if you use the plant and smoke it. Is the evidence that



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Lord Porter of Luddenham *contd.*]

we have at the moment better for the natural plant than it is for nabilone and dronabinol?

(*Dr Layward*) There are a number of issues here. First of all, there is a need, in the context of MS, for us to find out fairly quickly whether cannabis or cannabinoids can help with symptom control. The only way we are going to do that is for there to be clinically controlled trials. In the first instance, what we are proposing is we look at cannabis. Should that be shown to be efficacious, then we would go and have a look at a variety of different cannabinoids. It may well be that what one could do is have two arms to the initial trial, an arm with cannabis and with nabilone, for instance, and to be able to compare the two or, if one wanted to do a three arm, placebo, cannabis and nabilone, that is perfectly conceivable.

361. Cannabis is always smoked, I take it?

(*Dr Layward*) You can eat it.

362. The large numbers that are in these trials are presumably all smoking it, are they?

(*Dr Layward*) There are two small trials with cannabis. Cannabis was smoked.

363. There again, you immediately have a problem because it will be very, very difficult to get approval for it if it is smoked.

(*Dr Layward*) Absolutely. The route of administration is terribly important. Yes, that needs to be investigated. It is possible that it could be done by the oral route or the rectal route.

364. Are your tests going to be on those routes because, if not, you are wasting time on the smoking.

(*Dr Layward*) The clinical trials will have to be very careful as to which route the cannabis is going to be taken. Smoking is probably not the most attractive.

365. Is not this almost impossible because you are going to have to do it on live people and they smoke it. There are very few people, are there not, who would take cannabis except by smoking?

(*Dr Layward*) We have anecdotal evidence that people actually take cannabis by the oral route. They make cakes and take it by the oral route for their symptom control. In terms of designing a trial, the question that would come into it is who would be included on that trial. Would they be cannabis naive people—i.e., people who had not taken cannabis for symptom control before? It may well be that the design of a trial would have that as an exclusion criterion, for instance, if you have taken cannabis before, smoked it before, for your symptom control.

366. If the alternative trial of THC, nabilone or whatever did show positive results, then you are away. This could be accepted right away. There are not the problems of smoking. It is a pure substance. It is reproducible, which cannabis certainly is not and never will be, I suppose. The tests should take much less time because it is one substance you are looking at. Would that not be the better route to spend your time and money on?

(*Dr Layward*) That is certainly an alternative route and it may well be that we could have a number of arms to a clinical trial. The problem with just looking at THC is that is one of the psychoactive agents. One of the things that we do not want is to have unwanted side effects. That would be something that people

would have to take into consideration if they decided to go in the first instance to look at THC.

367. But you get that from cannabis because it contains THC.

(*Dr Layward*) That is correct, but I am informed that you can produce cannabis plants with a reduced THC content.

Lord Dixon-Smith] Is not the route to a final solution to this perhaps through the plant breeders rather than through a series of random experiments into different combinations of cannabinoids? If you can get the plant breeders to breed plants without particular cannabinoids so that you only have 50 of the 61 or 40 of the 61, provided you have the right ones, it might be quicker than doing the mathematical model which you are going to need to get through the combinations otherwise.

*Lord Soulsby of Swaffham Prior*

368. On the question of the health risks, in paragraph 6.9 of your memorandum, is it conceivable that the clinical benefit to individual MS sufferers outweighs any risks that they perceive and that you perceive exist?

(*Mrs Carlyle*) It is conceivable that the clinical benefit may outweigh the risks, but at this point obviously we have no scientific evidence on which people can make decisions. The main rationale of the Society is that we want to help people with MS to make an informed choice about therapeutic agents. They cannot do that if they do not actually know what the relative risks are.

369. Are they aware of the risks that they might be engendering by smoking cannabis?

(*Mrs Carlyle*) Indeed, many of the individuals I have spoken to have advised me that they are taking cannabis for therapeutic purposes and they have switched, for example, from smoking to taking a cannabis tea because they are concerned about the health risks, particularly in the light of evidence in relation to increased tar rates etc.

370. Do you, as a Society, put out information to MS sufferers of the comparative risks of smoking and how not to engender these risks?

(*Mrs Carlyle*) I regret it is an area in which there are great difficulties in that obviously we cannot be seen to condone or advise people in relation to breaking the law.

371. How do you get the message over?

(*Mrs Carlyle*) In many instances, people will read reports. It is an area in which many people with multiple sclerosis read a great deal. There is a great deal of information available, for example, on the Internet and some of the references within the British Medical Association report are utilised by people. If they are taking a drug for therapeutic purposes as opposed to recreational use, they are obviously taking in what evidence they can to make that decision.



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

*Lord Porter of Luddenham*

372. Do you feel clinical trial evidence is very poor and should be increased? How does one do this? How can proper trials be encouraged? Also, you mentioned financial disincentives that the pharmaceutical industry is being put off by and I would be very interested to know what these disincentives are.

(*Dr Layward*) The existing clinical trial evidence in MS is very limited. We are talking about six reports in the medical press of very small numbers. They are controlled but they are on a very small scale. Two were using cannabis—they smoked cannabis—and the other four were using oral THC or nabilone. We know that positive effects were reported for spasticity, for tremor, for spasms and nocturia. Negative effects were upon balance. Because of the small scale of these trials, because of the very variable and very unpredictable nature of MS, these are too small on which to be able to base any real knowledge of the efficacy of cannabis and cannabinoids. There is insufficient evidence for quality, safety and efficacy. We know that the anecdotal evidence certainly is invaluable as it informs but in itself is not sufficient scientific, objective evidence of efficacy. You asked about how clinical trials can be encouraged. I think clinical trials can be encouraged in a number of different ways. One of the ways is by raising awareness. This Committee, by sitting and taking this issue seriously, has played a part in making people aware of the possibility of the therapeutic uses of cannabinoids and cannabis and also to bring it out into the public eye and to have this discussed as a serious issue. The MS Society have taken this issue seriously. Last year, we organised a scientific conference with the Royal Pharmaceutical Society on the therapeutic applications of cannabinoids and, for the first time, brought together scientists, neurologists, clinical trials people, the pharmaceutical industry and people from the Home Office, to review the evidence and to discuss how we can move forward on this. Clearly, the BMA as well has been raising awareness. One of the things that has come out of the conference that we ran with the Royal Pharmaceutical Society is the development of a working party to bring experts together to decide on priorities and to decide how clinical trials can be pushed forward. The other way that clinical trials can be encouraged is clearly financial. The Society has said that we are willing to back clinical trials, a well designed and well controlled clinical trial that would answer the question of efficacy of cannabis in MS symptom control. Another way of raising awareness, in trying to bring this movement forward, is to try and get some good scientific, objective evidence that cannabis and cannabinoids can affect the symptoms of MS. I discussed earlier some of the basic science questions that we have been addressing. Those are the ways that we are working towards. It is raising awareness, encouraging, facilitating bringing interested parties together, and also saying that we are willing to provide financial backing to try and move this whole issue forward.

*Lord Nathan*

373. Dr Layward, has there been any difficulty in organising clinical trials on the subject which we have been discussing, arising from the need to secure a

licence from the Home Office and, if so, are they well disposed or not, or is this outside your experience?

(*Dr Layward*) Within MS, up until relatively recently, there has been little interest expressed in doing clinical trials on cannabis or cannabinoids. This has changed with increasing awareness over the last couple of years. We know of one organisation that has obtained the correct approvals. My Lord, one of the things you sent to us was from the University of Exeter. Their complementary medicine department have, I understand, gained approval for a clinical trial. Certainly I am aware that a small developmental pharmaceutical company has obtained from the Home Office a licence to cultivate and supply cannabis for research purposes and also a licence to supply for clinical trials. I understand therefore that getting Home Office approval for doing this is possible. One of the things that has been a problem is getting people interested enough. It is the attitude of researchers. They do not want to be associated with an illegal substance and something that would be considered to be on the fringe of scientific investigation. I think it is more the attitude that has been impeding either clinical trials or research, although I do understand licensing is difficult. You have to go through so many things to get these licences. It is not a particularly easy thing, but it is not impossible.

*Lord Walton of Detchant*

374. Of course, the anecdotal evidence—and it is only anecdotal—for preferring natural cannabis, however ingested, smoked or however taken, to the synthetics has never been fully tested in any kind of cross-over trial because although you set store very properly upon the importance of a double blind controlled trial comparing an active remedy against a placebo, there is a well hallowed technique of a cross-over trial in which you compare a particular remedy, following a wash out period, best known remedy which has previously been available. Surely, this is something that would be possible. Has anyone done any cross-over trials comparing natural cannabis with nabilone or one of the other synthetics? Secondly, from the American evidence that we have, the blood levels of THC achieved from all preparations of natural cannabis were extremely variable. The one which gave the best consistent blood levels was when administered by suppository. Has anyone carried out any trials using cannabis resin as a suppository?

(*Dr Layward*) In terms of the clinical trials into MS, which are very small and very few—there are only six of them—none of them did it by suppository. None of them have gone by the rectal route. What was the other question?

375. The first question was about cross-over trials.

(*Dr Layward*) None of those trials was a cross-over with nabilone versus cannabis. That has not been done.

376. Or indeed nabilone versus, for instance, baclofen or another drug for the treatment of spasticity? No such trials have been done?

(*Dr Layward*) No.



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

*Lord Porter of Luddenham*

377. I do not think you answered my question about the financial disincentives.

(*Dr Layward*) I think the issue is that the pharmaceutical industry is interested in running clinical trials that are commercially viable where basically they are going to make money out of it. I think development of new products is going to take many years. The issue we were talking about was in terms of looking at which cannabinoids and then perhaps making analogues of those cannabinoids and this could take really rather a long time. I think large pharmaceutical companies would have an incentive, in the long term, to look at novel cannabinoids should it look as though cannabis is efficacious in MS. In the first instance I think that needs to be done by the smaller companies that would look at the whole cannabis plant, but these are small developmental companies and would not have the financial backing to be able to take on everything from development of the whole plants, the drug development, the cultivation and looking at the contents and perhaps altering the contents of different cannabinoids within that, and taking on the burden of clinical trials as well. We are talking about small developmental companies and so therefore they would need to have other financial backers in order to take it through to a clinical trial. It probably would be then in that situation that the large pharmaceutical companies would have the incentive to go on and have a look at the different cannabinoids and then produce novel compounds that can be tested and then take those through to clinical trials. I think the issue is complicated by the whole plant as well as by the individual cannabinoids.

378. Yes, it is difficult, but they are not legal problems? The disincentives are not legal restrictions?

(*Dr Layward*) I do not think they are legal restrictions. I think they are much more to do with financial disincentives rather than legal.

*Lord Soulsby of Swaffham Prior*

379. One of the important things in any clinical trial is an adequate number of people. Reading your documentation I was somewhat amazed by the numbers you had for example in the anecdotal evidence in 4.1 and 4.2. You sent out requests via *MS Matters* and you only had 48 respondents and in some of your tables about MS symptoms it seems there is a very small number of people who would be interested in looking at the clinical aspects. What is the reason for this? Is it that they are afraid of declaring their interest because of the illegal side or that they are just not interested?

(*Dr Layward*) This information was asked for by letter and so they were actually putting their name and address to something and that is very hard for many people to do. I have taken many phone calls on cannabis and the helpline has taken many phone calls and the big problem is the fact that it is illegal and people are not happy about declaring that they are breaking the law. So getting the information, getting solid information is very hard in the use of cannabis.

380. So you think with a *bona fide* clinical trial you would generate much more interest and many more people?

(*Dr Layward*) Absolutely, yes.

*Lord Winston*

381. One of the things that we have heard in this enquiry is that a number of people get relief from their symptoms without psychoactive effects if they keep the dose sufficiently low. Therefore perhaps it might be easier to conduct a placebo trial on that basis because you would not necessarily know what you were taking.

(*Dr Layward*) The issue of placebos is a thorny one particularly when we are looking at something which has psychoactive effects. It is possible certainly to have a placebo-controlled trial. You would have to look at the different doses of cannabis in order to bring down the psychoactive effects. The other issue is if you have a large number of people and it is conducted so it is properly blinded, the power of suggestion is actually very strong and also the placebo effect in multiple sclerosis is very strong. We know that in terms of symptom control in other clinical trials. We also know in the recently beta interferon trials when asked about flu-like symptoms, which is a side effect of beta interferon, just as many people on the placebo said they had flu-like symptoms as they did on the active drug. We know the power of suggestion is very strong and certainly in the published trials on cannabis and cannabinoids in MS a number of authors actually commented that a number of people taking the placebo said they had psychoactive effects due to the placebo, so I do not think the placebo situation is going to be something that is going to be necessarily insurmountable. What we need to do is have large numbers and objective outcome measures to try and minimise any bias and it is, I suppose, possible that people might wish to look into the issue of some sort of psycho active agent as an active placebo or if we compared nabilone with cannabis then you would have another arm with a psychoactive agent. It is not an easy issue but it is not one that should stop us from going ahead with clinical trials because most of the drugs that are trialled do have side effects so people often have a good idea whether they are on the active drug or whether they are not.

382. Which outcome measures would you plump for given the nature of the symptoms which may change during the course of the disease anyway?

(*Dr Layward*) It is very difficult. It is such a fluctuating disease. Many of the symptoms are caused by different physiological reasons. The outcome measures would need to be objective and there are a number of outcome measures for spasticity, incontinence and tremor that are objective outcome measures. Pain is a little bit more difficult particularly because the pain in MS can be due to many different things. Sometimes it is neuropathic pains and sometimes it is pain from spasms. It is very variable. So the outcome measures need to be objective but also what is very important in MS is quality of life; there are quality of life measures specifically for MS that could be used as well. So I think it would have to be a mixture of quality of life with a good objective measurement of the particular



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued]

Lord Winston *contd.*]

symptom that people are going to focus in on at the clinical trial.

*Lord Walton of Detchant*

383. May I take it that no one has yet suggested that cannabis or nabilone or any of the other preparations has any clinical effect on the long-term course of multiple sclerosis? The effects that have been postulated have been solely those of relief of symptoms. If that is the case, bearing in mind the enormous variability of clinical course as between the relapsing form on the one hand and the progressive form on the other, in treatments which are designed to affect the long-term course of the disease such as, in the past, steroids, immuno-suppressants azathioprine and more recently interferon, it is necessary to recruit very large numbers. As you rightly say, however, there have been measures of specific clinical features which have been introduced and have been very effective for measuring, for example, spasticity. You can also record tremor on an accelerometer and indicate the extent to which that is being relieved by treatment. So, in fact, is it not the case that for symptomatic relief of individual symptoms you may not need such very large numbers in a cross over trial or even a double blind trial? (*Dr Layward*) On your first comment about affecting the course of the disease, there is no firm evidence that cannabinoids can affect the long-term course of disease. We are assuming that multiple sclerosis is an autoimmune disorder. There is theoretical information that a number of cannabinoids receptors are on immune cells and potentially could affect the immune system but I know of no firm evidence in EAE, for instance using the mouse model of MS, that it has altered the course of the disease. So what we are looking at therefore is not altering the course of the disease but looking at immediate symptom control. I agree very much with you on that. In terms of looking at the immediate efficacy on a symptom with an objective outcome measure, that could be done on relatively small numbers of people for immediate efficacy. However, one of the things that looks as though is happening from our anecdotal reports is that the long-term effects may tail off. We may get tolerance to cannabinoids, and also because MS is a lifelong illness you are likely to be taking a particular drug for a very long time, we also need to know the long-term effects and also, as I say, the tolerance build up. So we have to look at it in the short term for immediate efficacy of symptom control but also in the long-term in terms of side effects, risks, and tolerance.

*Lord Kirkwood*

384. You have already commented on the University of Exeter's Department of Complementary Medicine's pilot study. Are you aware of any other plans for large-scale trials?

(*Dr Layward*) We are aware of the interest of the University of Exeter in this pilot clinical trial in spasticity and very encouraged that they have got approval and are likely to go ahead in the near future. However, it is very difficult for us to comment at all

on it having not seen the design of the clinical trial. To our knowledge there is no other group within the United Kingdom which has formulated concrete proposals for a clinical trial of cannabis or cannabinoids in MS although a number have expressed an interest in doing so. We have knowledge of people who are interested in looking at the effects of cannabis and cannabinoids in pain and we also have knowledge of interest of some clinicians in looking at incontinence but we do not have the firm concrete clinical proposals as yet. It is very much in response to this lack of concrete proposals that we have been working with the Royal Pharmaceutical Society in order to get this working party together and get experts together to try and push this along and set priorities and encourage the clinical trials into symptom control of MS.

385. That particular pilot study is involved with cannabis alone, is it?

(*Dr Layward*) Yes.

386. Given what you were talking about earlier about the permission to grow the weed?

(*Dr Layward*) I am unaware of their source of cannabis.

*Chairman*

387. The trial they are proposing is on a controlled THC level?

(*Dr Layward*) I do not have details of the actual protocol of the University of Exeter, but I presume if they have got approval and got hold of cannabis for clinical use they would need to know what the THC content was. It would be a controlled THC content. They would need to have that basic quality evidence before going ahead.

*Lord Soulsby of Swaffham Prior*

388. There are some people such as the BMA and the Royal Pharmaceutical Society and others who want restrictions on the therapeutic use of cannabis and cannabinoids to be relaxed in advance of further research. Would you agree with their opinion?

(*Dr Layward*) The Society feels that we would only support the relaxation of restrictions on cannabis or cannabinoids in advance of further research if it can be shown that the present restrictions inhibit such research. As I described earlier, the present restrictions certainly make research more difficult but seem to impede research much more by influencing the attitude of potential researchers rather than actually in practicalities.

389. Coming back to the reluctance of individuals to participate because of the danger of being charged with having cannabis, it seems to me that you have to have some relaxation of the regulations before you can do the sort of thing that you want to have done.

(*Dr Layward*) Clinical trials can take place at the moment under the present restrictions and I am sure that people would be more than happy to participate. We have certainly had a lot of people saying to us they would volunteer for any clinical trial. If it was in a legal situation, people would volunteer for a clinical trial. What we are talking about at present is the



9 June 1998]

DR LORNA LAYWARD AND MRS RUTH CARLYLE

[Continued

Lord Soulsby of Swaffham Prior *contd.*]

situation of people smoking cannabis or taking cannabis orally in a totally illegal situation in their homes being very reluctant to come forward. It is a completely different situation when you have a clinical trial which is all above board and quite legal. I suspect there would be no problems at all in getting volunteers to come forward and take part in a clinical trial of cannabis. I really do not think that is an issue.

*Lord Walton of Detchant*

390. Let us suppose that some company were to take natural cannabis and were able to prepare a preparation of cannabis resin which if administered by suppository were capable of producing fairly recognisable standard blood levels of THC. If we could persuade the Home Office to consider licensing such a preparation, that presumably would make your life a great deal easier?

(*Dr Layward*) If it is shown that the benefits outweigh the risks and it is shown to help in symptom control in MS, that would be something we would very much look forward to.

391. Let me make it clear, easier in relation to trials?

(*Dr Layward*) It would be a way that could be done, yes.

*Chairman*

392. [Unallocated]

393. Is there anything you would like to add to what has already been said that we have not asked about?

(*Mrs Carlyle*) If you are interested in our views on the BMA report, my Lord Chairman, the MS Society is broadly in agreement with the British Medical Association report in that we agree that research is a matter of urgency, that controlled trials are needed on a larger number of individuals than is currently the case, that the administration, as we have discussed, is very important, that anecdotal evidence does not constitute scientific evidence, and that therapeutic use is a different use from recreational use. It is important in particular to emphasise that we agree that existing controlled clinical trials have been short-term studies and yet MS is a long-term condition. As we have said in our previous answers, this is a very important issue and I think it is important to emphasise that we are broadly in agreement with the BMA findings.

9 June 1998]

[Continued

**Supplementary Memorandum by the Multiple Sclerosis Society**

Q.345 *Relating to the prosecutions, can you give any indication as to the number of which you are aware and which courts, both geographically and by the status of the court, the matter comes before? Is there any geographical distinction?*

The MS Society has not been able to identify a source of data which distinguishes people with multiple sclerosis from other individuals prosecuted for possession of cannabis.

The following data is in the public domain:

*Number of prosecutions for possession of cannabis,  
United Kingdom 1986–1995*

| <i>Year</i> | <i>Number of<br/>Prosecutions</i> |
|-------------|-----------------------------------|
| 1986        | 11,493                            |
| 1987        | 11,878                            |
| 1988        | 14,049                            |
| 1989        | 17,654                            |
| 1990        | 19,281                            |
| 1991        | 18,470                            |
| 1992        | 14,875                            |
| 1993        | 18,846                            |
| 1994        | 24,025                            |
| 1995        | 24,386                            |

*Source:* Home Office, Crime and Criminal Justice Unit, Research and Statistics Directorate cited:  
Written PQs Hansard 20/01/1998 ref: 304 c514W.

The Multiple Sclerosis Society has not had the resources to conduct any separate monitoring of the situation. Our experience relates to individuals contacting the Society and to media reports. The numbers of individuals contacting the MS Society whilst going through the criminal justice system have been small, owing in part to the public stance of the Society as we do not encourage or condone any individual breaking the law.



---

TUESDAY 16 JUNE 1998

---

## Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.

Perry of Walton, L. (Chairman)  
Porter of Luddenham, L.  
Rea, L.  
Soulsby of Swaffham Prior, L.  
Walton of Detchant, L.

---

**Memorandum by William Notcutt, Consultant Anaesthetist; Mario Price, Senior Pharmacist;  
Patrick Blossfeldt, Consultant Anaesthetist; and Glen Chapman, Pre-Reg. Pharmacist, James Paget  
Hospital, Great Yarmouth, Norfolk.**

**CLINICAL EXPERIENCE OF THE SYNTHETIC CANNABINOID NABILONE  
FOR CHRONIC PAIN**

Presented at: Marihuana and Medicine conference, New York University Post Graduate Medical School,  
20-21 March 1998

and subsequently with appropriate modifications:

Plenary Lecture, Pain Society Annual Meeting, Leicester, 22-24 April 1998

This paper is supplemented with addenda by Dr Notcutt.

INTRODUCTION (ADDENDUM 1)

Chronic pain is widespread and its treatment can be one of the most challenging areas of modern medical practice. Patients may have a complex of biological, psychological and social problems. Their pain is commonly longstanding, and has often been poorly diagnosed and managed. They have usually been to a large number of doctors and had an even larger number of tests. Not surprisingly they have often lost faith with modern medicine.

Whilst there have been many advances in pain management there have been no radically new drugs in this field for more than a decade. Most advances have come in novel delivery modes or systems (eg Patient Controlled Analgesia, Transdermal Fentanyl etc).

Clinicians specialising in the management of chronic pain have become skilled in the use of a variety of drugs, many of which are not traditionally considered to be analgesics. Some of these include those with a significant abuse potential. In my own practice we frequently use opiates, antidepressants, ketamine and many other drugs unlicensed for use in pain.

THE INTRODUCTION TO THE USE OF NABILONE (ADDENDUM 2)

The Pain Relief Service at the James Paget Hospital, Great Yarmouth has a small staff of two consultant anaesthetists, three nurses and one psychologist (part time). It functions in a multidisciplinary mode by working closely with other services (eg orthopaedics, physical therapy) and support all pain relief activity within the hospital and out into the community. The usual problems of high referral rate, rapid turnover and limited resources are a normal part of everyday life.

Faced with patients who were untreatable by conventional therapy, one of the authors (WN) started to try the synthetic cannabinoid, Nabilone for a selected group. This as a result of anecdotal reports that cannabis can relieve the pain of Multiple Sclerosis (MS) and other painful problems such as chronic osteoarthritis. Nabilone was the only prescribable cannabinoid in the UK until 1997. It is only licensed for use for anti-emesis in chemotherapy.

All patients who have been considered for treatment with Nabilone have received extensive pain management in the past. This has been found to be either inadequate, unsuccessful, or in some cases unavailable. The patients were at "the end of the line" and there were no other options. As experience has grown, we have started to consider the possibility of Nabilone at an earlier stage.

Patients with a history of drug abuse or significant recreational use of cannabis have not been treated with Nabilone. However, we have discovered a number of patients attending our clinics who self medicate with cannabis for their pain. Advising on its use can be part of the pharmacological management of pain nowadays. In large cities this is becoming a normal and regular part of practice. The real drug abusers (heroin etc) remain almost impossible to treat for their chronic pains.

*16 June 1998]**[Continued]***PRESCRIBING NABILONE (ADDENDUM 3)**

We have evolved a method of using Nabilone. Initially we prescribe it at night-time so that any drowsiness merely enhances sleep. Most of the patients were suffering from significant sleep disturbance from their pain. The dose required seems to be variable. Sometimes we found that the 1mg capsule was too much. We therefore would reduce the dose to 0.25mg for some patients. As the patient's confidence in the drug was achieved, we would introduce it during the daytime as necessary. The highest dose that we have reached is 3mg/day.

All patients who have perceived some benefit from Nabilone have been subjected to a "start-stop-start etc" regime to establish whether the benefits are real. This would be the normal practice when introducing any other drug to a patient for the management of chronic pain. No placebos were used. No formal trial has yet been undertaken.

Sixty patients have been studied. The age range of most patients lies between 30 and 50 years. More females than males were treated reflecting the sex difference in a group of patients with multiple sclerosis. The patients have been divided into six groups for presentation. There is overlap between the groups, but from a clinical perspective it is easier to view them in this way.

**1. MULTIPLE SCLEROSIS. (ADDENDUM 4)**

About 50 per cent of patients with Multiple Sclerosis (MS) present with a variety of pain problems due to the widespread and variable damage that they suffer in the central nervous system. Whilst pain management can be relatively easy in the early stages it can become progressively harder and a few patients become unresponsive to conventional analgesic practice. When combined with other physical disabilities life can become very miserable for this group of patients.

Sixteen patients with advanced MS have been treated with Nabilone after the failure of conventional analgesic practice. Six patients have received benefit and three have continued to use Nabilone for up to three years. Two have a cluster of pains including neurogenic and retro-orbital pain and problems with muscle spasm. The third experienced mainly searing leg pains. Two of the three have deteriorated significantly from their MS. And one of those has recently discontinued Nabilone finding that she no longer needed it. The benefits for these patients have been analgesia, muscle relaxation, and sleep improvement.

Three patients gained benefit but discontinued Nabilone. Two found that cannabis provided better symptom relief both in quality of analgesia and dose control. A third obtained excellent pain control but developed a supra-ventricular tachycardia (she had experienced this spontaneously in the past). The final 10 patients with a variety of pain problems from multiple sclerosis obtained no useful benefit and some developed the usual side effects of dysphoria and drowsiness.

From the experience of this group of patients, we realised that further studies will require a much greater analysis of the different pains to establish what benefits there are.

**AETIOLOGY OF PAIN IN MS:**

1. Central neuropathic due to damage to pain pathways
2. Somatic muscle spasm due to damage to pathways controlling muscle tone
3. Visceral muscle spasm (eg bladder) (see above)
4. Mechanical (mainly spinal) due to loss of muscle function, strength and co-ordination
5. Other
6. Unrelated to MS

All of these may be aggravated by a multitude of psycho-social factors including depression, loss of mobility, increased dependence, terminal illness etc. Therefore a much more detailed analysis of the pain problems will be essential for future studies of cannabinoids in multiple sclerosis. The situation with AIDS patients is similar.

**2. CENTRAL NEUROGENIC PAIN**

Some of the most impressive records of the effects of cannabinoids on pain seem to be in the area of central neurogenic pain. Such patients have usually experienced substantial damage to the central nervous system and their pain is commonly very difficult to control.

A 62 year-old woman with de-afferentation pain secondary to a radio-frequency denervation of her trigeminal ganglion experienced uncontrolled pain on her right face. This was classical anaesthesia dolorosa. She had a range of assessments including neurological and psychiatric. She had a range of treatment including conventional antidepressant and anticonvulsant therapy. The trial of Nabilone achieved good control of the



*16 June 1998]**[Continued]*

pain and she was able to reduce her antidepressants. After nine months of Nabilone she was able to discontinue with no return of her pain. Unfortunately she was found at the same time to have a carcinoma of the kidney with significant destruction of the body of L1 by a metastasis. The malignancy was considered to be entirely coincidental. She underwent nephrectomy and radiotherapy (see below—"Malignancy").

A variety of other central neurogenic problems have been less successful. A tetraplegic patient obtaining pain control for his leg, patients found Nabilone of no use even though cannabis was highly effective. This was probably dosage related. An amputee following a brachial plexus avulsion has obtained temporary benefit, losing all his phantom pain whilst still continuing to work as a computer engineer. A third patient with a complex regional pain syndrome involving his chest and arm obtained significant relief and was prepared to accept some dysphoria as a trade off. Five other patients have not obtained significant help (cervical myelopathy, central cord injury, and thalamic pain).

### 3. PERIPHERAL NEUROPATHIC PAIN

Pain from peripheral neuropathies can be very difficult to treat successfully. They are usually poorly responsive to opioid analgesics and only some respond to anticonvulsants and tricyclic antidepressants.

Two patients with diabetic neuropathy and two with surgical nerve damage have been helped although I found the side effects of nabilone intolerable. A variety of other neuropathies have been tackled in four patients but without success (sensori-motor neuropathy, post herpetic neuralgia, post chemotherapy neuropathy, complex regional pain syndrome of arm).

### 4. MALIGNANCY

The pain of malignancy has become a comparatively easy problem to treat nowadays. The few patients now seen by the pain management service are those with the most complex problems.

A 45 year old male with an advanced bronchial carcinoma which had formed a tracheo-oesophageal fistula was experiencing severe upper anterior chest pain, partially relieved by morphine and other standard adjuvant therapy. Nausea and vomiting was also a major problem. He had had extensive surgery and was unwilling to go through any more invasive treatment. As a previous occasional user of cannabis he agreed to try Nabilone. He obtained significant improvement in his symptoms allowing him to cope better with his pain and circumstances. This enabled him to be managed at home for the last few weeks of life.

A 63 year old woman who had previously used Nabilone for anaesthesia dolorosa (see above) had developed a renal carcinoma with spinal secondaries. Surgery and radiotherapy had left her with the pain of a partially collapsed L1 vertebra. This pain was only partially controlled with morphine. She requested a further trial of Nabilone. 1mg at night has acted as an adjuvant to her analgesics and she maintains a good level of activity some two years after her original diagnosis.

From an experience of five patients it is difficult to draw conclusions. However, we have little doubt that cannabinoids may be an adjuvant to the well-established range of analgesics and other drugs that are used to control the pain of malignancy. They may avoid the need for expensive implanted analgesic systems for some patients.

### 5. SPINAL PROBLEMS

Spinal pain is the commonest problem presenting to all standard Pain Management Services. Out of this group the patients diagnosed as "Failed Back" (where the surgeons have failed to cure them) are the most daunting. They may have a combination of nociceptive and neuropathic pain complicated by major psycho-social disturbances.

Of 15 patients treated 10 probably obtained benefit with five continuing to use Nabilone for up to 2.5 years. Overall this group had the highest incidence of previous cannabis use and all preferred this to Nabilone. However, it must be pointed out that these patients had turned to cannabis for assistance but were not previous extensive recreational users.

A wide range of benefits (see below) has been seen but no specific tendencies could be identified, reflecting the heterogeneity of the group. Improvement in sleep and ability to cope has been more dominant than real analgesia.

### 6. "HEARTSINK PATIENTS"

Every Pain Management Service has its share of "Heartsink" patients, whose pain and psycho-social circumstances are so bizarre, distorted and dysfunctional that conventional therapy is wholly ineffective. Such patients can become substantial consumers of clinical time and there is a great temptation to offer them any new therapy that comes along in a desperate attempt to "do something".

*16 June 1998]**[Continued]*

Eight such patients have been treated with Nabilone. Whilst three perceived some short term improvement in sleep there was no justification for continuing therapy in any patient beyond an initial short trial. The temptation to use cannabinoids in this group should be resisted at this stage of knowledge.

#### SUMMARY OF THE RESULTS OF PATIENTS TREATED WITH NABILONE

We have treated 60 patients with Nabilone. 18 have obtained useful benefit, 15 have been equivocal or have experienced significant side-effects. 27 have obtained no benefit. A 30 per cent success rate would be considered poor by many standards. However, these patients were the worst pain problems of our service and do not respond to placebos.

#### SUMMARY OF THE BENEFITS OF NABILONE

This group of patients has been very heterogenous and it is difficult to draw many conclusions. Certain benefits of Nabilone were seen and most patients experienced more than one:

- a. Relief of pain
- b. Distancing of the patient from his pain, "Compressing" the pain
- c. Improvement in sleep
- d. Relief of Muscle Spasm
- e. Relief of Bladder spasms
- f. Relief of Constipation
- g. Relaxation and relief of anxiety
- h. Relief of misery, life more tolerable, relief of depression
- i. Mild euphoria

This list of benefits defines the main symptoms that need to be studied in the next generation of clinical trials of cannabinoids for chronic pain.

All patients who have tried smoked cannabis as well as Nabilone have found the former to be better. This may reflect both the intrinsic nature of the agents used and also the ability to accurately titrate the amount of drug.

#### SUMMARY OF THE ADVERSE EFFECTS OF NABILONE (ADDENDUM 5)

A large proportion of the patients we have treated have experienced side effects. Drowsiness and dysphoria have been the commonest and are the reason why many have discontinued the drug in spite of obtaining a benefit. The intrinsic properties of Nabilone, the difficulty of controlling the bio-availability, the inability to titrate the drug against fluctuations of pain through the day are all possible reasons for this. However, to set this within the context of chronic pain, these symptoms and problems are part of the normal spectrum of adverse effects that a physician will see from the analgesics, anticonvulsants, antidepressants and other drugs used for pain management.

Dependency is a major concern. However, we have only seen it occur in one patient. He gets mild withdrawal symptoms on discontinuation of Nabilone. These are far less in intensity than is seen with therapeutically used opiates and are also much less of a problem than those seen from benzodiazepine use. The only cardiovascular problem has been the precipitation of a supraventricular tachycardia in a patient susceptible to this.

#### FUTURE STUDIES (ADDENDUM 6)

Patients with chronic pain are a heterogeneous group. Therefore the classical double blind, placebo controlled studies are going to prove very difficult. Other techniques such as open crossover studies using each patient as his or her own control (N of 1) will probably be the next step forward. Studies of other drugs in chronic pain such as Amitriptylline may be appropriate models to follow.

The success of future trials will depend heavily not only on a satisfactory range of cannabinoids and cannabinoid mixtures (ie, plant extracts) but also on a range of delivery modes and systems (eg, Oral slow acting, inhaled rapid acting, suppository, parenteral etc). However, clinical studies on the analgesic properties of smoked cannabis are not only unnecessary and scientifically almost impossible to conduct but also medically, socially, and politically unacceptable.



16 June 1998]

[Continued

## CONCLUSION

This experience with Nabilone adds to a large body of anecdotal information on the use of cannabinoids for the management of pain. Whilst it produces no absolute proof, our evidence indicates that cannabinoids may well have a place in pain management and thus provides some signposts for the way ahead. Naturally further clinical trials are essential to establish the place of this potentially very valuable group of drugs.

The medical use of cannabinoids is a medical issue and should remain entirely with clinicians and scientists who are the only people who can determine the true place of these agents. If appropriate research programs are delayed by political and other outside interference, then many patients may be condemned to ongoing lives of unrelieved suffering when there is an effective remedy for some of their pains.

*Dr William Notcutt*

Consultant in Anaesthesia and Pain Management,  
James Paget Hospital, Great Yarmouth

Hon Senior Lecturer, School of Health,  
University of East Anglia

27 April 1998

## ADDENDA

I am supplementing the paper with some material from the file that I use for teaching on this subject. It is in note form but should provide additional background.

## ADDENDUM 1

*Two totally Separate Issues:*

*Recreational*

Legalisation of Heroin or Cocaine

Legalisation of Cannabis for  
Recreational Use

*Medical (Pain Relief etc)*

Use of Heroin and Cocaine for Pain  
Relief

Restoring and Evaluating Cannabis as  
a Prescribable Drug for Medical  
Purposes

There is no evidence that the medical use of heroin (Diamorphine) has contributed to the problem of heroin as a drug of abuse. Compare with USA and most other countries where heroin is banned.

*Historical use of Cannabis for Pain*

19th century experience (Hundreds of papers):

Neuralgic pain of arm, Sciatica, (hip, knee, foot), Inflammation of knee (*Donovan 1845*).

Facial Neuralgia, Rheumatic pain, sciatica, toothache (*Christison 1851*).

Facial pain, neuritis, migraine (*Reynolds*).

Dysmenorrhoea (*Queen Victoria*).

Anticonvulsant, Muscle Relaxant.

*Drugs used in Chronic Pain*

Drugs of potential abuse, unlicensed for use in Chronic pain:

Ketamine (Phencyclidine);

Transdermal Fentanyl and other Opioids;

Clobazam;

Amphetamine.

Other unlicensed drugs used in Chronic Pain:

Amitriptylline etc, most anticonvulsants, mexiletine, clonidine, steroids (epidurally).

16 June 1998]

[Continued

*Scheduled Drugs**Schedule 1  
Prohibited*Cannabis  
Opium  
Crack  
LSD/PCP  
Ecstasy*Schedule 2  
Prescription, Register  
Safe Custody*Dronabinol  
Heroin  
Cocaine  
  
Amphetamine*Schedule 3 +  
POM*Nabilone  
Codeine  
Lignocaine  
Ketamine  
Pemoline*Unlicensed use of Drugs Cited in the BNF*

Danazol (Anti-oestrogen)—Hereditary Angioedema;  
 Carbamazepine (Epilepsy)—Diabetes Insipidus;  
 Trimethoprim (Antibiotic)—acne prophylaxis;  
 Doxycycline (Antibiotic)—malaria prophylaxis;  
 Ovran (O/C)—emergency contraception;  
 Methoxsalen—PUVA skin sensitisation for Psoriasis;  
 Morphine in children under 12 years old; and  
 Azathiaprin (immunosuppressant)—wide variety of skin conditions (*BMJ*).

## ADDENDUM 2

*Pain Relief Service at James Paget Hospital, Great Yarmouth*

## Staff:

two consultant anaesthetists, three nurses, one psychologist (part time) multidisciplinary working;  
 Out-patients—600–700 new/year;  
 In-patient services—500 bed General Hospital;  
 Clinics—16 patients (average) per four hour session.

## Problems:

High referral rate.  
 Rapid turnover.  
 Fast response.  
 Limited resources.

*Cannabis Users at the Clinic*

Advising on the use of cannabis has become common as part of the pharmacological management of pain. But the real drug abusers are almost impossible to treat.

Palliative Care teams in London have a regular experience of advising their patients on their cannabis use and its possible interaction with other medication.

*Studying Nabilone*

Open Study in clinical setting.

No placebos.

Stop–start–stop etc.

Assessments within:

Normal clinics;

Normal clinical practice.

No formal assessment tools.



16 June 1998]

[Continued

## ADDENDUM 3

*Nabilone Dosing*

Nocte Initially 0.25–1 mg.

Highest: 1 mg tds.

Stop–Stop–Start.

Age 30–50 (range 28–82)

F &gt; M (mainly MS).

## ADDENDUM 4

*A Patient's view*

Dear Dr Notcutt

6 May 1997

... My pain is now constant, with no respite whether I am sitting in my wheelchair or laying in bed, the pain keeps me awake most nights and I feel that I am reaching breaking point. I did have a faint hope that there might be some surgical procedure that would cut the pathways to my pain centre, in the brain.

Thank you for your kind offer of making a home visit, but until such time that there is some change in the law that will enable you to prescribe the most affective drug, there is no need for a home visit.

Yours sincerely, Linda

*MS, Depression and Suicide*Clinicians should pay more attention to psychopathology (*BMJ Editorial* 20 September 1997).

Clinical Depression occurs in 50 per cent of patients at some time.

Suicide rate may be 2x normal.

Attention remains focused on physical neurological function.

*"Depression is a core symptom of MS and demands prompt and careful management."*66 per cent of MS patients suffer from Chronic Pain (*MS Society survey*).*Pain Syndromes in Ambulatory AIDS**Hewitt DJ et al, PAIN April 1997:*

151 Patients—1–7 pains (average 2.7) total: 405

Headache—46 per cent of patients, 17 per cent of pains;

Joint Pain—31 per cent of patients, 12 per cent of pains;

Polyneuropathy—28 per cent of patients, 10 per cent of pains;

Muscle Pains—27 per cent of patients, 12 per cent of pains.

Causes:

Direct Effect of AIDS Conditions—30 per cent;

Pre-existing unrelated conditions—24 per cent;

Therapy for AIDS—4 per cent;

Undetermined—37 per cent.

Pathophysiology:

Somatic 45 per cent;

Neuropathic 19 per cent;

Headache 17 per cent;

Visceral 15 per cent; and

Idiopathic 4 per cent.

Low CD4 counts related to polyneuropathy and Headaches

Headache, Radiculopathy—F &gt; M.

16 June 1998]

[Continued

## ADDENDUM 5

*Long Term Cannabis Use & Mental Health**British Journal of Psychiatry* 1997, 171:107-8.

## Dependence:

occurs in 30-50 per cent of regular users (cf morphine).

mild withdrawal symptoms; no progression.

## Psychosis:

Schizophrenic symptoms may be precipitated in susceptible individuals.

Chronic Cannabis use depresses motivation.

Gross structural Brain damage unlikely.

Cognitive Impairment occurs with chronic, heavy users (? reversible).

*Marijuana Use and Mortality*

65,171 enrolments in Medical Program, 1979-85.

Age 15-49 (ave 33).

F.U. 10 years average.

## Cannabis Use:

38 per cent Non-users;

20 per cent experiment;

22 per cent current use; and

20 per cent former users.

## Men:

Increased AIDS mortality;

Casual ? No;

Behavioural ? Likely.

## Women:

No significant increases.

## Note-Methodological Problems

*Am J Public Health*, April 1997, p 585-590.*Cannabis and driving**Influence of Marijuana on Driving*, HWJ Robbe, Institute for Human Pharmacology, Maastricht, Netherlands. ISBN 90 5147 023 1.

## ADDENDUM 6

*Future Studies*

Heterogenous group.

Start with current users of Nabilone (and ? Cannabis).

Open cross-over studies in each patient (N = 1).

Nabilone, placebo, cannabis extract, single cannabinoids.

Oral, rectal &amp; inhalational forms (SR + IR).

*Does TENS Work?*

"... Chronic pain is a different matter. Where the evidence is not clear cut, where some patients are seen to benefit, and where alternatives may not work for all patients, then carrying on using TENS until there is some clarification makes sense. That does put some heat on getting well-designed studies underway that are of sufficient power to provide practically useful answers."

*McQuay H et al BANDOLIER* March 1997 p 3 (on Evidence Based Health Care)

(\*\*\*)Also consider the use of epidural steroids)



16 June 1998]

[Continued

*Other Uses*

Muscle spasticity—somatic and visceral.

Adjuvant to opioid analgesia in palliative care—anxiolytic, anti-emetic, analgesic.

Appetite stimulant—AIDS, malignancy.

Glaucoma, Epilepsy, Asthma, Mood disorders.

*Future Possibilities??*

Acute Pain—eg acute back pain.

Sedation in Intensive Care.

Premedication.

**Letter from Dr David Lambert, Lecturer in Pharmacology, University of Leicester**

Further to your recent call for written evidence for the above select committee please find enclosed my evidence for your consideration.

My qualifications and relevant experience/expertise are noted below. I am a non-clinical lecturer in anaesthetic pharmacology in the Anaesthetics Department of Leicester University (based at Leicester Royal Infirmary). My interests in cannabinoids span around 5 years. I teach and have research interests in cannabinoid pharmacology. In addition, I was invited to give a plenary lecture to The Pain Society on cannabinoid pharmacology and to take part in a workshop on the same subject. Many of the questions noted in your letter were discussed and there seemed to be a general agreement that clinical trials on the use of cannabis/cannabinoids were essential.

The evidence that I would like to submit is;

1. Recent review written by myself and my colleagues and accepted for publication in British Journal of Anaesthesia (Labelled Appendix 1). Pages 8–12 are the most relevant with respect to medicinal use. (*not printed*)
2. Some additional comments and suggestions (Labelled Appendix 2).

If I can be of any further help or assistance please do not hesitate to contact me.

7 May 1998

**Appendix 2:****Additional Comments/Suggestions.**

1. Many of the questions posed in your letter have been discussed extensively in the USA. "The National Institutes of Health (NIH) has made available the report of the group of experts it convened February 19–20, 1997, to review the scientific data concerning the potential therapeutic uses for marijuana and the need for, and feasibility of, additional research". This report can be found as follows, <http://pharmacology.miningco.com/library/weekly/aa970906.htm> and I recommend that you seek permission for copying and distribution. Alternatively, if you feel it appropriate I would be prepared to summarise this report for you.

2. There are many potential therapeutic uses of cannabis/cannabinoids and the most important appear to be use in multiple sclerosis, nausea and vomiting and analgesia. There are many animal studies (see Appendix 1 page 9–10) suggesting analgesic properties but clinical data in man is lacking. This is an important area that must receive attention should cannabis/cannabinoids be available for medicinal use. The currently available analgesic agents (eg, opioids like morphine) have many potentially serious side effects such as respiratory depression. Cannabis/cannabinoids are in general devoid of these side effects and overdose is almost impossible. In addition Sanofi have developed antagonists for both the central and peripheral actions of cannabinoids (see Appendix 1 page 6–7) but these have not been used in man.

3. The overwhelming message coming from both the literature and discussion with clinical colleagues is that there is much evidence for a therapeutic role for cannabis/cannabinoids but that controlled clinical trials are essential to fully explore its use in different disease states. In my view these studies should be comparative with other accepted forms of treatment.

4. I feel that the debate on recreational use should be considered as a completely separate issue that must not be allowed to prevent the careful evaluation of cannabis/cannabinoids as therapeutic agents.

7 May 1998

16 June 1998]

[Continued

## Examination of Witnesses

DR WILLIAM NOTCUTT, Consultant Anaesthetist, James Paget Hospital, and DR DAVID LAMBERT, Non-clinical Lecturer in Anaesthetic Pharmacology, University of Leicester, were called in and examined.

*Chairman*

394. Welcome, gentlemen. Can you start by introducing yourselves and telling us how you come to be interested in the therapeutic use of cannabinoids?

(*Dr Notcutt*) My name is Dr William Notcutt. I am currently a consultant anaesthetist at the James Paget Hospital in Great Yarmouth. I qualified in 1970. I have been a Fellow of the College of Anaesthetists since 1976. I have been a consultant in anaesthesia and pain relief since 1982. I have had an interest in that time in pain relief and in palliative care. I am currently the director of pain relief services at our hospital. During that time, I have done quite a lot of research, as much as one can do in a district general hospital these days with the pressure of work. I did a substantial paper on patient controlled analgesia, looking at the use of diamorphine post-operatively for patients. We studied 1,000 patients on self-administration. I am currently in a project on back pain research and improving back pain services. As a side issue, I have developed an interest in cannabinoids and their use over several years of trying to find something else to help some of the poor, miserable patients that flood into my pain relief clinic regularly every week. About a month ago, I presented my work that I have been doing over the last few years at a plenary lecture at the Annual Pain Society meeting in Leicester.

(*Dr Lambert*) My name is Dr David Lambert. I am a non-clinical lecturer in anaesthetic pharmacology at the University of Leicester. I work in the department of anaesthesia which is based in the Leicester Royal Infirmary. I obtained a PhD in 1987. Since then, I have been interested in understanding how receptors work with a particular interest in inhibitory receptors. For the last six years, I have been working on the opioid system and have been interested in trying to understand how analgesics work, particularly the way in which these drugs interact with receptors by modification receptors, and by looking at pathways that come beyond the receptor. In the latter few years, I have developed an interest in the cannabinoid system in that this is also an inhibitory type of receptor. It has very many similarities with the opioid system. I think that there are clear advantages for this system for the treatment of pain and perhaps we will get to some of those points through the discussion. I also presented a plenary lecture at the Annual Pain Society meeting in Leicester on cannabinoids.

395. Can you comment on how you select patients for nabilone and the strategy you use in administering the drug and determining an appropriate dose?

(*Dr Notcutt*) I think first of all we need, just for a moment, to reflect on who these patients are that I have been using nabilone on. These are patients with chronic pain, which is a complex of biological, psychological and social problems. The common features of these are that their pain has been very longstanding. It has often been poorly managed and poorly diagnosed. The patients have often been

everywhere; they have had every test. My clinic is often the last resort. This is the group of patients that I have been looking at and studying. Many of these patients have been using opiates, drugs like morphine and similar drugs, and may still even be on them, but still not achieving satisfactory pain relief to provide them with a reasonable quality of life. I need to put that picture clearly and then say what we have moved on to. The doctors who specialise in pain relief are well used to using a very wide range of drugs in rather unusual circumstances, including drugs that are otherwise unlicensed for chronic pain. I can give you a list if necessary. The sort of patients that we have been using Nabilone on have all been getting inadequate pain relief with all the conventional treatment. They are unsuccessful in getting a good quality of life. These are the patients that I have selected. My first one or two patients had multiple sclerosis. That was partly my lead into this area because of the anecdotal reports that have been coming out for many years on the benefits of cannabis in multiple sclerosis. We have gone very cautiously by using the drug, starting it out just using it at night time and recognising that it may have significant effects on sleep and on other aspects of the patients' wellbeing, and then studying and watching them over the following days and weeks to see what impact it has had on them, on their pain, on their distress, on their sleep patterns and other aspects of their life. We have titrated the drug into the patient, observing the effect against side effects and things like that. When patients tell us they are getting good pain relief we will then stop and see what happens and then start again. This is a normal practice for any pain clinician, when he is using, as I have been, nabilone, antidepressants, anticonvulsants or a wide range of other drugs that are used in our practice.

396. Is nabilone exactly the same as the other pain relieving substances that you try in the sense that it only works in some circumstances?

(*Dr Notcutt*) Yes. I would say that with every single drug that I prescribe. It will work in some circumstances; it will not work in others, and that goes for morphine as well.

*Lord Walton of Detchant*

397. Is your custom ever to use nabilone alone or are you using it consistently in combination with other standard analgesics?

(*Dr Notcutt*) It is my normal practice when I am introducing another drug to a patient that is otherwise stable on their medication, that I do not take them off their previous medication. Otherwise it becomes very difficult to evaluate what the effect is.

398. You are using it as an add on?

(*Dr Notcutt*) Yes, and then maybe subtract another drug later. If they are getting good quality analgesia, I may then withdraw other agents that they are on and that are supporting them.

399. Can you give us an overall impression of the therapeutic benefits that you have observed in



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Lord Walton of Detchant *contd.*]

patients treated with nabilone and, in particular, which clinical pain conditions are likely to respond best to this treatment?

(*Dr Notcutt*) I looked at all the patients that I have treated with nabilone and I categorised them into basically six groups. I will start with the patients with multiple sclerosis because there has been quite a lot of interest in this particular group. My results have been that about 50 per cent of patients have actually had some beneficial response, but only about 30 per cent have continued on the drug itself because of side effects. The others have said, "Yes, this has helped me but no, thank you very much. The side effects are intolerable", and this goes with morphine and most other drugs as well.

400. What adverse effects of the drug most severely limit its usefulness therapeutically and can you, with any reasonable degree of confidence, disentangle the psychoactive effects of the drug from the pain relief aspect?

(*Dr Notcutt*) There are two effects, most commonly. One is dysphoria, a feeling of unreality which every single patient who has experienced it has complained about and said, "No, I cannot tolerate this". The other one is drowsiness. Those are exactly the same side effects I see with opiates, with antidepressants and anticonvulsants, all standard drugs. These are all very normal, common side effects I see with drugs, using them in chronic pain.

401. Finally, would your patient population treated with nabilone include what is often referred to as psychogenic regional pain such as atypical facial neuralgia, for example?

(*Dr Notcutt*) If I can go back one step, perhaps one major group of patients who seem to have benefited from cannabinoids—and this is partly a multiple sclerosis group—are those where there is substantial nerve damage, where the pain is due to nerve damage. The broad division of pain is pain from, say, an arthritic joint where the nervous system is intact and transmitting pain from that damaged joint or that damaged or diseased part of the body. Then are those pain states due to actual damage to the nervous system itself, of which multiple sclerosis is a classical example. Shingles pain, post-stroke pain are other examples.

402. You do not recommend it for patients with the psychogenic syndrome such as atypical facial neuralgia?

(*Dr Notcutt*) Here, we have a problem of definition of what is meant by "psychogenic". I have great difficulties with accepting that there is such a phenomenon as actual psychogenic pain. I prefer the term idiopathic pain. Where they have a psychiatric disease that is causing pain, then this is an inappropriate way to treat the psychiatric condition. Atypical facial pain may be a pain problem that we should look at because there are a lot of patients out there who do not get benefit from any conventional treatment.

Lord Dixon-Smith

403. Presumably, when a patient does have adverse effects, in the end, you are relying on a patient's subjective judgment and if they say it is intolerable then you will obviously take them off and on to something else. I can well understand that. Have you any evidence by way of comparison between nabilone itself, which of course is itself a pure extracted cannabinoid, and people who actually use the cannabis plant, which is of course using a big combination and, if it is smoked, taken in a very different way?

(*Dr Notcutt*) The population I treat are in rural Norfolk. I am not working in an inner city environment. I have only used it on patients who I am 100 per cent sure are not abusing drugs.

404. I see.

(*Dr Notcutt*) Several patients that I have used nabilone on have also tried cannabis as well. These are normal individuals within society and not from those groups heavily into the "drug culture". With one exception, all of them have said that cannabis gave them better quality analgesia than the nabilone did. This may be due to two things. It may be an intrinsic effect of cannabis against nabilone. There is some evidence that the mixture of cannabinoids may interact. It may be better to have a mixture of cannabinoids than just a single one; or it may be that the delivery system—i.e., they have been smoking it—is a better way of delivering the drug. In fact, it is a very much more accurate and effective way of delivering the drug than by mouth. I would add that I am not promoting smoking the drug; I am merely making the observation that smoking is a more accurate way of delivering it. We could do the same with inhalers or whatever.

Lord Soulsby of Swaffham Prior

405. From your experience, do you believe that nabilone should be licensed for the treatment of pain?

(*Dr Notcutt*) It is licensed as a drug for us. I would say that there are very few drugs that I use in the treatment of chronic pain that are actually licensed for chronic pain. I should think 80 or 90 per cent of the prescriptions done by doctors who are involved in chronic pain are using drugs in an unlicensed fashion. Whether it has a licence or not is neither here nor there. If, in time, we find that pain control an indication and good, solid clinical trials come out and say, "Yes, this is useful for this particular condition", then so be it. That is not going to stop me at present practising what I already do.

406. Are there any plans to undertake controlled clinical trials with this aim and, as a supplementary to that, how difficult would it be to undertake such trials with a psychoactive drug?

(*Dr Notcutt*) Conducting clinical trials on this particular group of drugs, or any drugs in chronic pain, is intensely difficult. By way of background, I looked through six recent copies of the journal *Pain*, which is the leading pain journal in the world. Of 106 papers in these six journals, only 40 were clinical papers and, of those 40, only six were controlled clinical trials. Of those, only one was in chronic pain.



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

That is an index of the difficulty of doing controlled clinical trials. I see there is a way forward in doing it. There are clinical trial techniques, using patients, for example, as their own control. We can put them on the drug and take them off, maybe insert a placebo, maybe compare nabilone with an extract of cannabis, or two or three different extracts of cannabis, so that the patients act as their own control in evaluating the effects.

407. One of the questions I was going to ask you was about delivery of the drug in such trials. I was interested to hear you say that smoking is the most effective way of quantifying the delivery.

(Dr Notcutt) No; of delivering the drug.

408. But not quantifying?

(Dr Notcutt) No, because from the doctor's point of view it is impossible to quantify it. From the patients' point of view, they can quantify it because they smoke until they reach their end point. It is exactly the same as patient controlled analgesia with diamorphine (or heroin) in an electronic pump, with a button by your bedside when you are having a hip replacement.

409. In a trial, you would rely on the patient to determine the level of quantification of his drug receipt?

(Dr Notcutt) But we do that already. We do that post-operatively. Every hospital is doing that right now with patients after operations. They are titrating themselves. They are giving themselves as much as they need of heroin or morphine etc.

410. But in this theoretical clinical trial? We have heard from other witnesses that it is very difficult to quantify the dose.

(Dr Notcutt) It is very difficult to quantify the dose that is for each particular patient. Chronic pain patients are a very mixed, heterogeneous group of patients. They are very different. There are not two that are the same and this makes a big problem with doing any comparative study. I am involved currently in a study of an opiate. It is very difficult to do really good research on this type of thing. Every patient is different. The chemistry of their brains is different. Therefore, in some ways, I have come to the conclusion personally that the patient acting as his own control is the best way forward. Every patient I have seen who has been using cannabis, who has been smoking it for pain relief, has said to me they can give themselves exactly enough and they do not want any more. They are fed up with the pain dominating their life. They just want to move the pain out of the way so that they can then actually get on with their life. They do not want to spend it in a dysphoric ("high") state.

411. Who would you expect to sponsor and undertake such research? Is there sufficient interest in the clinical community to support such research?

(Dr Notcutt) If I answer the second question first, there is a huge amount of interest in the pain relief community across this country, judging by the interest we had at the Pain Society meeting we were at last month and also the response we have had subsequently. I have a lot of people ringing up and saying, "We want to be in on this", reflecting that we have had fundamentally no new drugs for pain relief

for 20 years. We have had new delivery systems but we have actually had no new drugs for pain relief. This is a whole new generation, a whole new area that is just beginning to have potential.

412. Who would sponsor it?

(Dr Notcutt) Who sponsors any research? We have to go round and find the people to provide the money for it. The patients are there. The physicians are there. We have got to put some money together from whatever sources so that we can start this off. Maybe the Medical Research Council will come forward. Maybe other research bodies, whether it is our local, regional consortia, will fund it. I have every intention of approaching them to provide the resources for this.

Lord Dixon-Smith

413. I regret that this happened since we had the MS Society in front of us and I would rather have wished to cross-examine them, but I do have some contacts with that Society. I have had a complaint from them that they in fact were not getting adequate information about properly based experiments, which they would be prepared to sponsor. The applicants simply were not coming forward. They exist in this field and presumably should be well known. Dealing with cannabis is, in effect, dealing with an illegal substance, and therefore requires a much more sophisticated licensing procedure. Is this the reason why this sort of work is not being applied for?

(Dr Notcutt) I think you have answered your question yourself. This is the reason why. My pharmacy colleagues and I have worked very hard to try and find our way through to conduct some research. We were doing some work with nabilone. We wanted to take it on potentially to set up and do comparative studies with nabilone and with other cannabinoids. The actual logistics of doing it, the licensing system and the availability of a medicinal grade compound deliverable in an acceptable, medical fashion are almost insurmountable. The news from last week, of soon having the availability of medicinal grade cannabinoids to work with, will allow us to start to put together the studies. Why spend hours putting together studies if at the end of the day they founder (they have founded, I gather, in the past with other people) because of the licensing and the sheer logistics of getting materials? Now we have the opportunity to put studies together, so groups of us can do multi-centre studies and really get some good work done on this and to go to the MS Society with firm proposals. There is no point in their complaining. No one has been able to produce the studies. There is a lot of other research which is a lot easier to do!

Lord Soulsby of Swaffham Prior

414. In your list of people who might support you, you did not say anything about the pharmaceutical companies.

(Dr Notcutt) I have talked to pharmaceutical companies for ten years on this. Geoffrey Guy has eventually seen the way forward and has actually



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

looked into this and said, "Yes, I can set something up". Why have the giants not done so? I do not know all the commercial pressures, but part of it has just been the sheer difficulty of actually doing research with a Schedule 1 drug.

*Lord Nathan*

415. Is it possible to indicate to us how long ago it was that you or Mr Guy started the application to the Home Office for a licence, and when it was actually granted?

(*Dr Notcutt*) Dr Guy came on board when he attended a meeting that I had with Professor Wall and others with the minister in December last year. Until that time, Dr Guy had been at one meeting in July when he had shown a passing interest. In December, he joined in with his experience and came along with us to talk with the minister. He realised, in talking with the Home Office, and with his knowledge of licensing of plant based medicines, that there possibly was a way through. He talked to the right people, asked the right questions and the result is what happened last week.

416. Was the licence granted last week?

(*Dr Notcutt*) I have not had communication with him beyond what I have seen on the Internet and in the press. He tells me that he is the possessor of a licence for growing and producing medicinal grade extracts of cannabis. Whether he knows he can get it or whether it is actually in his hand as a piece of paper signed, sealed and delivered, I am not sure.

*Lord Butterfield*

417. The Medical Research Council, in general, has made very few approaches to people to do research. The whole ethos of the Medical Research Council has been that people who had a problem on their mind would come forward for support. I hope that has not been an impedance to you and your colleagues to go to the Medical Research Council saying, "We have the patients and we have got the problems".

(*Dr Notcutt*) The exciting thing now is we have the patients. We now know where to start looking and we now have materials that we can put together for studies to come to the Medical Research Council, or to whatever funding body we can find, with substantial clinical trials and clinical studies that will actually stand up, are valid and will produce us the information that we need to pursue this further.

418. The important thing about the new development is they are going to grow the cannabis. Presumably they are going to do the same old studies that were done years ago in Mill Hill into digitalis. You just have to accumulate material and get a grade as to effectiveness. That is something which the MRC have experience of doing in the past.

(*Dr Notcutt*) The plan that Geoffrey Guy has is that the materials he will be using will be standardised materials. He will use standardised plants (cloned) that have a standardised cocktail of cannabinoids.

419. At Mill Hill, the standardisation was done by the Medical Research Council. To get hold of standardised material, you have to have a group of people to do the standardisation.

(*Dr Notcutt*) Dr Guy has his own laboratories to produce standardised materials and also analytical laboratories to check on that. Basically, it is growing from cloned plants which will produce standardised mixtures.

*Lord Walton of Detchant*

420. The fundamental question is this: once you have that standardised preparation, presumably somebody is going to have to do some pharmacokinetic studies. In the actual documentation from Dr Guy, he identifies ten separate cannabinoids. What we do not know is, bearing in mind evidence that has been given to us that natural cannabis is preferable in many respects to the synthetics such as nabilone, which of these cannabinoids prove to be the most effective for these trials. In order to be able to get a standardised preparation, you also have to have an opportunity of measuring blood levels to see whether the actual bio-availability of the substance is constant or relatively constant. At the moment, I am told the only blood levels that can be measured are the levels of THC. The question is whether you have any information to suggest that the other cannabinoids can be measured in blood as well.

(*Dr Notcutt*) The answer to that last point is no. As far as I know, that has not been developed. I have great concern about getting too hung up on measuring blood levels because we already know, for example, that it is a pointless exercise measuring the blood level of morphine to establish how much pain relief somebody is getting. It is a very individual thing. It is only comparatively recently we have gradually let go the drug papaveretum, which was a mixture of opiate alkaloids. This mixture is derived directly from opium, of which one of the constituents was morphine. There is still a substantial body of opinion in this country that believes that papaveretum is a better opioid than morphine itself. It is a standardised preparation. These would be standardised mixtures of cannabinoids.

*Lord Porter of Luddenham*

421. You have been talking principally about nabilone which you have been administering and your experiences with it particularly. Now we have got on to standardised plant material and so forth. Nabilone is a single, synthetic compound whose structure is known. It is now being used in treatment. Are there any others?

(*Dr Notcutt*) Available at the moment?

422. Are there any other synthetic cannabinoid related compounds which are being used therapeutically?

(*Dr Notcutt*) The only other one that is theoretically available in this country, although practically I do not believe it is, is the drug dronabinol.

16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Lord Porter of Luddenham *contd.*]

423. That is not synthetic, is it?

*(Dr Notcutt)* Technically, I think the marketed dronabinol is synthetic.

424. They extract it?

*(Dr Notcutt)* No, they do not extract it. They synthesise it.

425. Is it all synthesised?

*(Dr Notcutt)* That is what I am led to believe.

426. Have you any experience of this being compared with nabilone?

*(Dr Notcutt)* No. We wanted to do a trial on that and we actually got hold of some but the company provided us with material that was out of date, which was rather unfortunate. There are studies done in the United States with dronabinol alone and it is licensed against sickness; the other licence is for AIDS wasting syndrome, to help people put on weight.

427. Is this one of the reasons why you have stuck to nabilone, because it is licensed and dronabinol is not?

*(Dr Notcutt)* It is. There is another, purely economic, one. I have major problems even funding what I have been doing with nabilone. Dronabinol is a major increase in money terms.

428. Can you say why dronabinol should not be licensed and nabilone is?

*(Dr Notcutt)* It is licensed. It is a Schedule 2 drug in this country. Interestingly, nabilone is Schedule 3<sup>1</sup>. From what I gather, they have very similar effects but I do not really know of any controlled studies. The books will say they have essentially the same effects and the same side effects but there really are not, as I know it, any good, comparative studies with patients.

429. Are there any other synthetics, apart from nabilone, or perhaps dronabinol, which have been tested therapeutically?

*(Dr Notcutt)* Not that I am aware of.

430. So we are in the market either for those two or for a complex mixture of plant materials?

*(Dr Notcutt)* Yes.

431. These complex mixtures are standardised only for the TCH content, are they not?

*(Dr Notcutt)* No. They are standardised right across the spectrum so that you will know how much Delta 9 THC, how much cannabidiol etc is in the mixture. In other words, you will have the whole spread of cannabinoids.

432. Every one of these is standardised? They have analysed for 60 cannabinoids and 300 other compounds?

*(Dr Notcutt)* They will be at that point, yes. That is what I am led to believe. That is the only way you can get a licence to produce it as a medicinal product. You have to be able to give the "fingerprint", if you like, of what the mixture is.

433. I am glad I do not have the task.

*(Dr Notcutt)* I share that view, yes.

434. In your very useful report on page two you were talking about cannabis. You said, "Advising on

cannabis use can be part of the pharmacological management of pain nowadays. In large cities this is becoming a normal and regular part of practice." This is a rather surprising statement to me. Can you explain?

*(Dr Notcutt)* I have discovered it in my part of rural East Anglia on occasions, talking to patients. Once they actually realise that I am not going to have a go at them for smoking, they will talk to me. Actually finding out what they are using is as important as knowing what other drugs they are using, so I do ask direct questions. However, I work in palliative care and I talked to some nurses recently at a conference who worked in south London. They said, "That is a normal part of our talking to patients and finding out about patients. It is not only finding out what drugs they are on, but also what they are smoking with their cannabis and maybe advising them on it".

Chairman

435. Can I turn to the receptor system? Has anyone to your knowledge contemplated using endogenous anandamide?

*(Dr Notcutt)* As far as I know, people have speculated on this. I do not know how available anandamide is to do clinical trials. We have morphine which we use. The ligand in the body is beta endorphin and, as far as I know, there have been no clinical trials on the use of beta endorphin at all.

436. That is an exception. Adrenalin has been used for a very long time.

*(Dr Notcutt)* Correct. As far as I know, there is none available. It will be something that people will want to do. The only way you can get it is to synthesise the molecule and then produce a medicinal grade product which can then be used. That is way outside my remit to be able to comment any further.*(Dr Lambert)* The short answer is that, to my knowledge, nobody has used or contemplated the use of anandamide clinically. However, conceptually, it is a very good idea in that delivering the endogenous agonists of the receptor directly to the receptor makes good sense. However, if you carefully examine the literature, anandamide has not been detected in human plasma, human CSF or in human blood products. The substance is broken down very rapidly at the site at which it is released. In terms of giving it clinically, its rapid metabolism I think would preclude its use. If you did want to use it clinically, where exactly would you put it? If you injected intrathecally, extradurally or if you gave it intravenously, it would likely be broken down before it reached its target receptor. There are hydrolysis resistant forms of anandamide like metanandamide which is relatively resistant to breakdown. However, it is incredibly insoluble. To contemplate using that clinically would be very difficult. If we look at the anandamide system, anandamide is an endogenous cannabinoid that is synthesised and released in the central nervous system. There is now a compound which is available to inhibit the re-uptake of anandamide, so it is possible that we could potentiate the anandamide signal by giving this uptake inhibitor. However, the toxicology of this compound has not, to my knowledge, been studied. It seems to<sup>1</sup> This is incorrect. Nabilone is not a controlled drug.



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Chairman *contd.*]

work in animal models but again where would we actually inject this compound? As a final statement on the anandamide story, perhaps we ought to look at the non-steroidal anti-inflammatory drugs, particularly Ibuprofen. Ibuprofen inhibits the breakdown of anandamide and it is possible that we may be able to use non-steroidals perhaps to enhance the anandamidergic signal. However, some of you may know that the non-steroidals cross the blood brain barrier very poorly. I think there is some potential there but, as for administering synthetic anandamide to human beings, I think that would be fraught with problems and it would be very difficult.

437. Which drug firm claimed the discovery of anandamide? Whereabouts was anandamide first isolated?

(*Dr Lambert*) None. Anandamide was identified in porcine brain by Devane and colleagues. This was a collaborative venture encompassing Israel and the United Kingdom.

438. I see.

(*Dr Lambert*) Nevertheless, it is an important issue, the antagonist story. The National Institute of Drug Abuse has begun a collaborative project funded by NIDA and Sanofi. They are beginning trials of the central cannabinoid antagonist in man. There is no data actually available yet. Before coming to this meeting, I did write to Madame Mosse from Sanofi. I understand that she is the project coordinator for that compound. Unfortunately, she has not yet replied. I would suspect that some of these studies have been done in man. If we are trialling antagonists in man, to add to some of the comments made earlier, I would suspect that there is a large number of pharmaceutical industries who have cannabinoid agonists that they are perhaps considering trialling in man. You asked Dr Notcutt what other synthetic cannabinoids had been tried in man. Quite rightly, there are none, but if you look in the animal literature there may be ten or twelve synthetic cannabinoid agonists. They have not been tried in man but my own hunch is that these may be lead compounds for the pharmaceutical industry. I would suspect that they have cannabinoid agonists that are ready to begin trialling in man.

*Lord Porter of Luddenham*

439. Why do you say "Quite rightly they have not been tried in man"?

(*Dr Lambert*) The current legislation makes it very difficult. I think it is nothing more than that.

*Chairman*

440. One would imagine that the companies would have tried them if they felt there was any hope?

(*Dr Lambert*) In contrast to the evidence that we have heard on man, a lot of which is anecdotal and based on personal experiences of clinicians, the animal story is completely different. I think it is now clear that there are many situations in which cannabinoids can relieve symptoms of disease. For example, the nociceptive action of cannabinoids given intrathecally, extradurally, rubbed into the

skin, given subcutaneously etc. It seems that just about every route that you can give cannabis or cannabinoids to an animal, you will produce some form of analgesia. That can be at spinal and supraspinal sites. The animal evidence is very, very strong for a therapeutic indication for these drugs but, in terms of what we see in man, it is anecdotally based and basically what patients tell their doctors. The animal studies are very well advanced in that area and I think if you have heard evidence from Dr Pertwee he may well have expanded that far more eloquently than I have.

*Lord Butterfield*

441. At the end of your review article you say, "Perhaps it is time to be bold and even consider extradural administration". What advantages might this offer over the other routes that you have been talking about?

(*Dr Lambert*) If you accept that the psychotomimetic effects that you see with cannabis and cannabinoids come from supraspinal sites—i.e., they are higher than the spinal cord—then it is quite clear that, if you put the cannabinoids directly into the spinal cord, provided you can prevent rostral spread, it is likely that you will be able, for example, to produce analgesia without any of the troublesome psychotomimetic effects. There have been some studies done by Lickman and Martin in the United States who have shown that, if you inject about 300 micrograms of THC into the spinal cord of a rat, you get very good analgesia and very little spread rostrally. Of course, clinically, we could get round that by making the cannabinoid hyperbaric hence leaving it at the site in which you inject it. I think it is a very interesting concept of putting these into the spinal cord so we are getting analgesia without any of the psychotomimetic effects. We need to set aside the risk, for example, of infection of the cord with long term use of that. Should we inject intrathecally or extradurally?

(*Dr Notcutt*) This is very similar to the effect we have with opiates. For pain relief, often you can get away with very much lower doses without the central effects of opiates by injecting them into the spine. The only problem is that the technical difficulties of running these systems mean that you finish up, long term, with possible infections and a whole host of other side effects.

442. How long do the extradural injections last?

(*Dr Notcutt*) It depends. You might do them just after an operation for two or three days. It gives a very high quality pain relief, although there are a fair number of side effects and problems.

443. Is this with an infusion pump?

(*Dr Notcutt*) Yes, or, for example, with a patient with chronic pain, they have systems chronically implanted and they have a very high problem rate. Implanted systems, for long term use, into the spinal cord with people injecting through the skin into ports that lie underneath the skin, will work quite well but they have a high problem rate.

444. When you say "into the spinal cord", you mean extradurally?



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

*Lord Butterfield contd.]*

(*Dr Notcutt*) Extradurally, which is outside the dural sheath, but also into the cerebrospinal fluid which bathes the spinal cord.

445. Is that what you mean by "extradural administration"?

(*Dr Lambert*) In the review article, we meant extradurally, putting it around the meninges, in that that form of administration avoids puncturing the dura and reduces the risk of recurrent infection. Provided the drugs are very lipid soluble, I do not see any major problems in administering them extradurally.

*Lord Walton of Detchant*

446. Surely anything that goes into the cerebrospinal fluid diffuses and will ultimately reach the brain, even though its primary effects may be upon the spinal cord. Extradural administration can only in principle affect the spinal roots or the spinal nerves as they come out through the dura. Is that not the case?

(*Dr Notcutt*) No. The best model we can use is opiates, with drugs like morphine and various other opiates. You can still get away with a very much lower dose for the relief of pain and much higher quality pain relief by using these drugs outside the dura. So they pass through the dura and into the cerebrospinal fluid. Alternatively they can be put into the cerebrospinal fluid itself. You do get central effects as they will be absorbed. They will be picked up by the bloodstream and they will have an effect on the brain, but this is at a very much lower level than one would expect if one were to achieve the same level of pain relief by injecting it into a vein or taking it by mouth.

*Lord Rea*

447. We have already discussed Dr Guy's project. I wonder if you could go into it a little more deeply and particularly tell us about your involvement with GW Pharmaceuticals and Dr Geoffrey Guy?

(*Dr Notcutt*) May I make it clear I have no commercial involvement with Geoffrey Guy at all. He is somebody who I met six months ago who, for my part, having thrown my weight against a door that seemed to be not shifting, suddenly came along with the key and opened it. That is my only relationship with him. He has started to move forward. I have provided him with information. I have provided him with a protocol from a research project that we have put together to use as part of his submissions. I am now wanting to get together a group, liaising with him, because he needs the clinicians out there to be working with him as he develops his product. He needs the clinicians there, ready to take it on and to move it on into the clinical field.

448. Could you tell us a little bit about the protocol which you developed which he is presumably using as the basis of his clinical trials?

(*Dr Notcutt*) He used a protocol that we drew up and put through an ethical committee, which was a basic N of 1 type of trial. I am getting together with

a group of other clinicians. There would be no great point in getting together whilst we have not had any products to use. There has been tremendous difficulty with this. We are at the starting point here. Although I have done quite a lot of work on this, I am wanting to get together with some colleagues in academic institutions to put together a group, certainly within the Pain Society, which can actually develop one or more protocols. In particular, I think we need an evaluation protocol that looks at the drug in an individual and sees how they respond maybe to one or more cannabinoids. Then, if they respond and they are doing well on it, we need the long term studies to start to look at these agents over a much longer term. I already have patients who have taken nabilone for three years or so. That is where I see it going.

449. What sort of numbers of patients are you thinking about for the second stage?

(*Dr Notcutt*) I think as many as possible. Geoffrey Guy is quoting a figure of 600 patient years.

450. Before you get to that stage, presumably you have to have some permission from the Medicines Control Agency? Although apparently Dr Guy has passed through the Home Office barrier, what about that one?

(*Dr Notcutt*) That will have to be done. From his side putting together the material, we will have to do the work to put the trials together, to present them to the relevant authorities. We are at the starting point at the moment.

451. Are you hopeful that this can be achieved?

(*Dr Notcutt*) I have been in this area for about the last four or five years now. I have been more hopeful in the last two months. I have seen more happen since Christmas time than in the whole of the previous time I have been involved in this. I suspect that more has gone on in the last six months perhaps than has gone on, in clinical terms, in the last 20 years.

452. I wonder if you could expand a little bit on the nature of the extract that is envisaged? Also, I think Dr Guy has said in his statement that he is going to work on new methods of administration too. What about those?

(*Dr Notcutt*) I am not privy to everything Dr Guy has suggested but I think he will get a pure extract from his various different cannabis clones and he will maybe have four or six. I do not know how he will determine that. Then, he will have a pure medicinal product. Initially, trials will be on the oral use because that is an easy, common way of using the substance anyway. The technology to use it in an inhaled form, which gives a much more precise end point and better absorption, will be a little more difficult. It is not quite as easy as putting it into an aerosol and firing it in. I am not a pharmacologist, but various papers have been done on aerosoling cannabis extracts into the lungs for the treatment of asthma and so on over 20 years ago. It is quite feasible, but we will need the long acting preparation, which you would take by mouth. A lot of patients who have MS, if they have acute increases in their pain, may need something which is quick acting, particularly to titrate themselves up to a level that they want. Again, the parallels with opiates are there.



16 June 1998]

DR WILLIAM NOTCUTT AND DR DAVID LAMBERT

[Continued]

Lord Rea *contd.*]

I prescribe my long acting opiate by mouth; I have my quick acting with opiates as well to deal with those peaks of pain that patients need to deal with.

453. Will this work be done with a product before it is fully standardised in the way that we were discussing earlier, with each of the components measured?

(*Dr Notcutt*) No. If it is going to be a medicinal product, it must have its actual fingerprint of what it contains in it.

454. This will be part of the research?

(*Dr Notcutt*) He will say, "Here is product A, product B, product C". I may want to do a study just on product A. I may want to say, "Here I have a patient who is willing to embark on this". So maybe

they will start with nabilone as a gold standard and then compare it with product A, product B, product C or product D with different levels of cannabinoids and different mixtures of cannabinoids. There is some evidence out there: for example, that patients with MS get better symptom control with certain types of cannabis.

455. You will be able to measure the spectrum of the different cannabinoids in product A, product B and product C?

(*Dr Notcutt*) Yes.

Chairman] We have to thank you very much indeed for all that you have told us. It has been very interesting indeed.

**Memorandum by Dr Philip Robson MB, MRCP, MRCPsych, Consultant Psychiatrist, Warneford Hospital, Oxford, Senior Clinical Lecturer, University of Oxford**

#### CANNABIS AND CANNABINOIDS AS MEDICINES

1.1 I was commissioned in 1996 by the Department of Health (DH) to conduct a critical review of the scientific literature pertaining to therapeutic uses of cannabis and cannabinoids. Primary sources were identified from reference lists supplied by DH and the Institute for the Study of Drug Dependence, a Medline literature search, and from evidence presented in books, reports and review articles revealed to me by clinicians and academics with first-hand experience of cannabinoid research. The subsequent report<sup>1</sup> has been subject to peer review, and I am informed by DH that it has been submitted to the Select Committee. The main conclusions are as follows:

1.2 Cannabis has been valued as a medicine for more than 8,000 years in a wide range of applications. This use has ranged throughout Asia, the Middle East, China, South America, Africa and Europe. Twentieth century moral attitudes and legal restrictions in response to widespread recreational use have severely inhibited the scientific evaluation of a possible role for cannabis and its derivatives within modern therapeutic regimes.

1.3 Dozens of active constituents of herbal cannabis have been identified, and the complex interactions between these "cannabinoids" are not well understood. Some therapeutic cannabinoids are not psychoactive (mind-altering).

1.4 The recent discovery of receptors for cannabinoids on cell membranes both within the brain and outside it, and the identification of a naturally-occurring chemical ("anandamide") which binds with these receptors is a major scientific advance, and raises exciting possibilities for new drug development. The biological significance of the "anandamide system" has yet to be evaluated, but it may impinge upon mood, cognition, co-ordination and posture, and pain perception.

1.5 Natural cannabis, its main active ingredient (delta-9-THC), and synthetic analogues of delta-9-THC are effective in reducing or preventing nausea and vomiting. There are no comparisons with modern 5HT<sub>3</sub> antagonists. A preliminary study suggests that delta-8-THC may be particularly effective in children.

1.6 Many individuals suffering from neurological disorders which produce painful spasticity (such as multiple sclerosis) claim that both natural cannabis and delta-9-THC relieve spasms and other unpleasant symptoms, and improve general well-being. There is some scientific support for these claims but further investigation is required. Anecdotal reports of anti-convulsant activity await confirmation.

1.7 There is preliminary evidence that delta-9-THC is an effective pain-killer, at the expense of a high incidence of sedation.

1.8 Natural cannabis and several individual cannabinoids lower intraocular pressure in normal people and patients with glaucoma, though unwanted effects limit clinical utility in many patients studied to date.

1.9 Preliminary studies suggest that delta-9-THC and other cannabinoids may reduce anxiety and improve sleep.

1.10 Natural cannabis and delta-9-THC have a certain number of beneficial effects in people suffering from AIDS or certain cancers in that they are anti-emetic, analgesic, anxiety-reducing, sleep enhancing, antipyretic, and appetite-stimulating. This is perhaps one of the most compelling areas for future research.

16 June 1998]

[Continued

1.11 A number of historical applications and properties identified from research in animals await evaluation in humans.

1.12 Cannabis and cannabinoids frequently produce unwanted effects in clinical studies. Typically, these include sedation, intoxication or mental clouding, clumsiness, dizziness, dry mouth, lowered blood pressure or increased heart rate. These effects are much better tolerated in some clinical conditions (eg cancer, MS, AIDS, chronic pain) than others (eg glaucoma). Cannabis is extremely safe in overdose.

1.13 Standard treatments for many of the above conditions are unsatisfactory, either through lack of effectiveness or toxic effects. The therapeutic potential of cannabis must be judged in the context of strengths and weaknesses of these existing treatments.

1.14 A recent poll suggests that the majority of British doctors believe that cannabis should once again be available on prescription.

1.15 Controlled and co-ordinated human research on cannabis and cannabinoids is required to determine more accurately optimal dosing schedules and routes of administration, to delineate and quantify the therapeutic and adverse effects with more confidence, to examine further the interactions between the various active constituents of herbal cannabis, and to explore the natural role of anandamide and the cannabinoid receptors. This research will only be possible if the regulations imposed under the Misuse of Drugs Act are made more flexible.

1.16 Pharmaceutical development of non-psychotropic cannabinoids might lead to useful new medicines.

2. In my opinion, existing evidence is sufficient to justify the prescription of cannabinoids in certain medical conditions, and the provision of "compassionate reefers" to patients with AIDS and certain cancers.

3. I have received many anecdotal reports from patients that cannabis relieves anxiety, assists sleep, eases the symptoms of opiate withdrawal, and stimulates appetite. I have recently obtained local Research Ethics Committee clearance to carry out pilot studies using nabilone and THC (as dronabinol capsules) as an adjunct during inpatient and community detoxification from opiates, and as a short-term anxiolytic and hypnotic in patients with acute drug-related problems.

#### PSYCHOLOGICAL RISKS OF CANNABIS

4.1 I have been responsible for the development and clinical supervision of the Oxfordshire Regional Drug Dependency Service since 1990. Quite apart from this professional experience, my interests outside medicine have resulted in my having many friends and acquaintances over the past 30 years who are regular recreational cannabis users. Cannabis, like any other drug, undoubtedly carries real risks alongside its beneficial or pleasurable effects. Based on my personal observations in a professional and private context over many years, however, I believe there has been a tendency to exaggerate the psychological risks posed by moderate cannabis use, often on the basis of anecdotal or unconfirmed reports which would be rejected if they related to positive rather than adverse outcomes.

4.2 According to the Oxfordshire Regional Data Base, 83 per cent of patients presenting to the Oxfordshire Drug Dependency Unit in 1997-98 reported using cannabis, but only 4.9 per cent were referred because of cannabis-related problems. This figure is consistent with National statistics.

5.1 With another investigator I conducted an interview study<sup>2</sup> of 581 amphetamine, cocaine and heroin users, of whom 380 (65 per cent) had never had any contact with police or helping agencies in connection with their drug use ("invisible" group). Eighty seven per cent of the invisible group and 83 per cent of the contact group smoked cannabis, more than two-thirds of them on a daily basis.

5.2 The level of addiction to the various drugs in the two subject groups was assessed by means of a well-validated measure, the Severity of Dependence Scale (SDS)<sup>3</sup>. Scores of less than five are generally associated with drugs of low addictive potential. SDS scores for cannabis were 2.6 in the contact group and 3.4 in the "invisible" group. For comparison, the scores for LSD (generally accepted as of very low addictive potential) were 3.1 and 1.1 respectively, while those for heroin were 12.9 and 5.6.

#### REFERENCES

1. Robson P (1998) *Therapeutic aspects of cannabis and cannabinoids*. Reported to be lodged in House of Commons Library.
2. Robson P, Bruce M (1997). A comparison of "visible" and "invisible" users of amphetamine, cocaine and heroin: two distinct populations? *Addiction* 92, 1729-36.
3. Sutherland G, Edwards G, Taylor C et al (1986). The measurement of opiate dependence. *British Journal of Addiction*, 81, 485-94.

Dr Philip Robson

26 May 1998



16 June 1998]

[Continued]

## Examination of Witness

DR PHILIP ROBSON, Consultant Psychiatrist, Warneford Hospital, Oxford, called in and examined.

*Chairman*

456. Welcome. Can you introduce yourself briefly and tell us how you came to be interested in cannabis?

(*Dr Robson*) I am Philip Robson. I am a consultant psychiatrist in Oxford and also a senior clinical lecturer in the department of psychiatry at the University of Oxford. I qualified in medicine in 1970 and worked as a hospital doctor and a clinical pharmacologist before training in psychiatry. In 1990, I was appointed to develop and run the Regional Drug Dependence Unit in Oxford which I have been doing since and which is now well and truly up and running. My current research interests range from the neuropharmacology of craving for opiates to field work on invisible drug users, which investigates how they differ from drug users that we actually meet in clinic. The other thing perhaps of relevance is that, for six years, I was on the Research Ethics Committee in Oxfordshire, representing the university. My interest in cannabis from a professional sense started, I suppose, when I was a hospital doctor and I met the first patient who said that he used cannabis to relieve symptoms from MS. He was an in-patient and the ward sister was so impressed that she allowed him to find nooks and crannies in the ward to indulge his self-medication. I felt she was such a classic of her kind, a statuesque London sister of the old school and, frankly, if it was good enough for her, it was good enough for me. I was very impressed and from then on I have had many patients tell me that, for one reason or another, cannabis has been useful. Perhaps the most startling of all—and this is a true anecdote—is that two weekends ago I was playing golf with an 80 year old retired physician. We were held up on the twelfth tee and I was astonished when he took out of his pocket a battered tin and rolled himself up a cannabis cigarette. I said, “What on earth is happening?” He said, “I find it helps with my balance and coordination”. I really cannot comment except to say that he did beat me, so it certainly did not do him any harm. On a personal level, I was a medical student in the sixties and I had a parallel though subsidiary career in music and that brought me into contact with many people who smoked cannabis in a recreational sense. Some of them I still know today. I have quite a wide familiarity with the recreational use of cannabis. Clearly, since I have been running the Drug Dependence Unit, I have met a lot of patients who smoke cannabis as part of a wide range of drugs use. I suppose the most obvious thing about those patients is that they are so very different to the average person who smokes cannabis recreationally. One of my main hobby horses really is that we know so little about drug use in the community, what one might call real drug use, as opposed to the visible drug use that happens when people develop drug related problems or get arrested. There is a huge lack of knowledge, especially about cannabis use, in a non-pathological way. That was a rather rambling introduction, for which I apologise.

457. We have seen your recent report on the therapeutic uses of cannabis and cannabinoids,

commissioned by the Department of Health. Are your conclusions broadly similar to those reached in the recently published BMA report on the same topic?

A. They really are, with one exception which I will come to in a moment. I am very relieved about that because these were two independent exercises. The review that I did started in 1996 and finished in 1997. I did not have any access to the BMA work. Independent analysis does seem to come to the same conclusions about the available research. The only area where I perhaps do differ is on the matter of smoked cannabis, which I think you are going to cover in later questions, but generally speaking I completely agree with the conclusions reached by the BMA.

*Lord Soulsby of Swaffham Prior*

458. Can you comment on the possible therapeutic uses of cannabis and cannabinoids from your own clinical experience? Also can you explain how they can be used in detoxification from opiates and other drug-related problems that you mention in your memorandum?

A. Amongst patients that I see presenting to the Drug Dependency Unit in Oxford, symptoms like extreme anxiety, sleeplessness, lack of confidence about the steps that they are thinking of taking and just the plain difficulties of detoxing from mainly opiates but other drugs as well are an every day experience for me. Obviously, this can usually be handled in a non-pharmacological way by reassurance, by other strategies that one has, but there is nevertheless a need for a pharmacological treatment of these particular symptoms. Of course, one normally falls back on benzodiazepines which are highly addictive and have other shortcomings. It is an area of interest as to whether nabilone or other cannabinoids might be useful in this area. I have had permission from the ethics committee and clearance to do pilot studies of nabilone in anxiety and as a hypnotic—very short term interventions, of course. These are encouraging but they are only pilot studies and controlled research is of course urgently needed. I would perhaps categorise those as minor indications. A major indication lies in the field of AIDS medicine, patients who present with symptomatic HIV related disease. Here, it seems that cannabis and cannabinoids do have a particularly useful profile. This is one of the greatest areas of interest that came out of my review: possible application of cannabis and cannabinoids in patients with terminal diseases like this which are so unpleasant in terms of the range of symptoms suffered over weeks and months. Vomiting, weight loss, pain, great anxiety are commonplace amongst AIDS patients. There are no effective treatments. The use of cannabinoids has always to be seen in the context of strengths and weaknesses of existing treatments. It is no use seeing them in a vacuum. You could argue that treating anxious drug addicts may be a relatively low priority since there are at least other strategies which are available. However, for



16 June 1998]

DR PHILIP ROBSON

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

AIDS patients, I think there really is not anything which can meet the same need. Although I see far fewer patients in that category, that is the most compelling indication that I have come across from my own personal point of view.

*Lord Rea*

459. Are you talking about smoked cannabis for the AIDS patients?

A. Certainly smoked cannabis is the one I hear about anecdotally. Of course, in America, the one controlled study that has been done on this was with dronabinol, oral, synthetic THC. It was highly effective, effective enough to convince the highly sceptical FDA that this was a valid indication. It is smoked cannabis that one hears anecdotally about constantly from patients.

*Lord Walton of Detchant*

460. You hinted that you disagree with certain aspects of the BMA report on smoking cannabis and of course not only from that report but from many other sources we have had a good deal of evidence to suggest that the hazards of smoking cannabis do not differ very significantly from those of smoking tobacco. There are problems not only of chronic bronchitis and other complications and potentially an increased risk of carcinoma of the lung, but also various immune changes in the lung which relate to alterations of T lymphocytes and so on. How can you justify the smoking of cannabis as a medical treatment?

A. I would only attempt to justify it in a very selected group of patients. With regard to the immune effects, this is a very important effect clearly for the AIDS arena. We do not have the information we need and we must get it. The evidence that we do have is reasonably reassuring in that the one study that followed quite a large group of people with HIV infection over 18 months did not demonstrate any correlation with smoking cannabis and progression to symptomatic disease. It is very weak evidence but at least it is reassuring to some extent. I totally accept the unacceptability of smoked cannabis for many patients, but there are areas I think in terminal care, for example, where it is not a consideration that one has to concern oneself about. To me, seeing a patient in pain, in distress, in a hospital ward, unable to get a drug which they have found in their own home to be helpful is a simple affront to humanity. As a doctor, I would feel extremely uneasy about that. There was an interesting hypothetical case described in the BMJ quite recently of an MS patient who was admitted for a period of respite care, who had lived with his mother and had been accustomed to having cannabis supplied by his mother, which of course he found very useful. When he came into the hospital, the staff found themselves in a terrible quandary because, unlike the sister that I referred to all those years ago, they really cannot collude with an illegal practice. The mother bakes a cake and brings in the cake for the patient. The patient becomes much more content and happy. The ethical dilemma that was highlighted was should the staff analyse the cake and discover

and confirm that cannabis is baked into it, or should they pretend not to know. It is a ridiculous situation, in my view. It does affront me as a doctor that patients in that particular extreme condition, perhaps in extremis, can have access to a Brompton cocktail but not cannabis if they want it. I am not aware of any clinical pharmacology that would support the effectiveness of a Brompton cocktail but of course we all intuitively know that it is helpful in certain conditions. We do not have any more information on cannabis but we intuitively know that it can help in certain conditions.

461. We have had a good deal of information to suggest that oral administration is in some respects unsatisfactory because of hepatic breakdown of the cannabinoids but some information has come to us suggesting that administration by suppository is likely to be much more effective and will give you a higher blood level of THC. What would your view be about the acceptability of suppository administration as an alternative to smoking?

A. If we were living in France, I would not have any problem with that at all. I agree that it would be difficult to put across to English patients. I think Professor Iversen has mentioned to me that this is a very possible route of administration and Dr Notcutt of course mentioned aerosols. With a bit of ingenuity, I think it will be possible to bypass the oral route without the problems of smoked material.

*Lord Butterfield*

462. As a consultant to a drug and alcohol dependence unit, how serious a problem do you consider addiction to and dependence on cannabis to be?

A. I certainly see it from time to time. In my written evidence, I gave some figures though which put the situation into perspective. I think the figure is 4.9 per cent of patients who presented to our service over the last year listed on the data collection form cannabis as their main drug. Even that is an ambiguous statement because cannabis may be your main drug in the sense of the one that you enjoy most and smoke most, but it may not be the one that is causing you the problems that are bringing you to the drug dependence unit. If anything, I suspect that is an over estimate, but even if it is the correct estimate, it approximates to the national reported level of about six per cent. Yes, it does occur. Psychological dependence certainly occurs, but my own feeling as a clinician and as a researcher—and I also mention the piece of research that I did with Malcolm Bruce which attempts to quantify the dependence liability of a range of drugs in both visible and invisible drug users in the community using a snowballing technique—is that the information that comes from that, using quite a well validated measure, is that the drug falls well below the threshold of what would be expected from a dependency producing drug which has clinical significance. The other interesting strand on this is that there have been some surveys of especially young people who are regular smokers which attempt to distinguish the once only from the once or twice a week and the more frequent smoker. One example of this is the so called ESPAD study



16 June 1998]

DR PHILIP ROBSON

[Continued]

Lord Butterfield *contd.*]

which looked at 26 European countries and young people and their drug use across a wide range of contexts. What is striking is that the vast majority of people do smoke cannabis in a moderate or even less than moderate way, a sort of transient way. They might use it once or twice or a proportion will use it three or four times a month, something of that order. That actually is the majority of people. Only a third of people in that survey had used cannabis more than six times in the last month. The measures of the severity of dependence scale and the clinical experience that one has about what people really do in the real world out there do suggest that this is not a powerful drug of addiction at all.

463. The other question that was posed to you was whether you could assess the dangers of cannabis as a drug of addiction in relation to other addictive agents. You have told us your views about cannabis but you are a man who sees other things too. From what you are saying, it sounds to me, a complete ingenué, that certain other compounds that people take are much more addictive than six a month.

A. I do not meet people who are prepared to knock over old ladies in the street or burglarise houses or commit other crimes to obtain cannabis. They may be out there, but the drugs that I am preoccupied with are the stimulants and heroin. These are the drugs that develop the level of dependence which actually forces people to take steps to obtain a drug when it is not there. Cannabis smokers may be dependent, but if the cannabis is no longer available, in my opinion, most of them would simply stop smoking and perhaps drink more alcohol.

464. That would also fit with the way people smoke when they are students but seem to drop it when they get a job.

A. Yes. That is probably absolutely right. The other thing of course is the complication of tobacco. Perhaps most people smoke cannabis rolled with tobacco, so there is the tobacco addiction included in that. In fact, it used to be said that one of the worst side effects of cannabis smoking was becoming dependent on tobacco smoking in the longer run.

Chairman

465. You mentioned the figure of 4.9 per cent. Have you any comparable figures for other drugs of addiction?

A. Yes. The vast majority of patients presenting are dependent on heroin. Heroin would be something like 75/78 per cent. About a third, 20 per cent or a little more than that, would be amphetamine or cocaine. Cannabis would be next. Then you have just the odd person who would present with a difficulty with ecstasy or something of that sort. Overwhelmingly, it is heroin and opiates that people present with at drug dependency units. However, that does not necessarily mean very much because obviously they present for two reasons. One, they are having problems and, two, presumably they think that the drug dependency unit can help them in some way. If I have a drug problem and I think they are not going to be able to meet my needs, I will not present and then it will not appear in any statistic. It is a

confused figure and it should not be taken as a prevalence measure really.

Lord Butterfield

466. What about tobacco or nicotine?

A. In our new contract culture, I am afraid that we are not paid to treat tobacco problems, even though tobacco kills 150,000 people a year in the United Kingdom. We do not really do it at all, I am afraid, so I just do not know. Tobacco actually has the highest hit rate of addictive substances. Something in the region of 85 per cent who smoke a single tobacco cigarette will spend a period of time under an addiction to cigarettes at some stage in their lives so it is an awe inspiring substance.

Chairman

467. It seems to differ enormously between individuals. I suppose that is true with everything.

A. That is very true. One of the very striking features of the study I did with Malcolm Bruce in invisible and visible drug use is how much lower the addictive potential of all the drugs, including heroin, amphetamine, is in people who are invisible, who are in other words just quietly using the drug without getting into trouble with the police, coming to see doctors or whatever. There are many reasons for that which I will not go into now but, yes, it is very much an individual related thing and an environment related thing.

468. Some people are able to get themselves off the problem without help.

A. Absolutely, even with heroin and even with crack cocaine.

Lord Kirkwood

469. In your written submission, you make the statement that existing evidence is sufficient to justify the provision of compassionate reefer to patients with AIDS and certain cancers. Was there any specific reason you did not include MS sufferers in that?

A. No. One of the problems is the problem raised by Lord Walton, the difficulty of smoked cannabis in patients who may have a very long or a normal lifespan and then the risk of introducing an iatrogenic element to this. Having said that, I think that patients should be largely treated as responsible for their own choices and given the choice perhaps to run a risk which is defined, a very clearly stated risk, if they feel that the benefits given by the drug are sufficient.

470. Which indications have you in mind when you are offering a compassionate reefer?

A. I think we have probably covered them. It is mainly conditions like AIDS, certain cancers in their later stages, perhaps MS, perhaps other illnesses in which the quality of life sinks to such a level that people might well be prepared to take a risk to alleviate symptoms.

16 June 1998]

DR PHILIP ROBSON

[Continued]

Lord Kirkwood *contd.*]

471. How would you administer the system of giving out the reefer? Do you think this is a practical proposal?

A. I do. Rather than the law deciding who should have a drug, the doctor and his or her patient should have that power. You could, I suppose, have a licensing system similar to the heroin licensing system if there was concern about making this available to all doctors, although I would personally not have any concerns about that myself. If a doctor genuinely believes that cannabis or cannabinoids would be of benefit to the patient, the patient having fully considered the risks and benefits that the doctor explains fully, perhaps in a written form of consent, I find it objectionable that the law prevents that therapeutic partnership from accessing the drug. I do not think it would be very difficult to return to a situation that, after all, was in existence in this country so few years ago, relatively speaking.

Chairman

472. You would apply that equally to the synthetic cannabinoids and to the cannabis plant?

A. In the current state of knowledge where we have this wealth of anecdotal evidence that the smoked substance is more than the sum of its parts perhaps, I would. In the sort of coordinated research that I think is needed, I hope we will find out quite quickly much more about these other cannabinoids that are now synthesisable and it may not be necessary, in a few years' time I hope, to use such a crude thing as herbal cannabis; but until that time, whilst there is at least anecdotal evidence that it is more effective, it just is not a dangerous enough drug for me to want to ban it.

473. I spent a lot of time in my younger period running the Department of Biological Standards and that is why I made the comment that the trial was still at an early stage if standardisation was going to apply to all the substances in the extract. It means that there is a very long gap during which your compassionate reefer is required.

A. Exactly. I think it is urgent that this work should happen because we must not forget why it was that cannabis fell from favour early this century. It was really related to this lack of consistency, the variability in potency, the poor storage characteristics it has and the alternative synthetics that had appeared. It is a huge issue but I would hope the period would not be too long. In the meantime, I think it is an affront to humanity not to make it available.

474. The other thing was the dropping of it from the rescheduling and the fact that it was said to have no therapeutic value.

A. This may have been in relation to the stability and the potency problems.

Lord Walton of Detchant

475. Even in the 1970s an American drug company marketed nabilone and, having done so, after two or three years it withdrew it from the market because it was just not being prescribed to be a sufficient

commercial success. Can you look back and explain why you think that may have happened?

A. I think cannabis has become very unrespectable. I think it is not really taken seriously, especially at that time. Perhaps nabilone is not a very good drug. It is a synthetic drug which I think differs in many ways from the substance it is modelled on.

Lord Porter of Luddenham

476. Do you feel it is important that cannabis extracts, cannabis products, as well as synthetic cannabinoids like nabilone, should be made available for future clinical trials?

A. I do because I think we have to work out whether the apparent advantage of smoked cannabis is related to route rather than the actual mixture and the interactions of the various constituents. I think it is right to say that most of the studies—and there are not very many—in which cannabis has been compared with a cannabinoid the cannabis has been smoked and the cannabinoid has been oral. That is a very unfair advantage I think because smoking is such a fantastically efficient way of getting the drug on board and into the brain. We do need some research on that and, as part of the programme of research which is going to be required, we need some clinical pharmacology studies to tease out various basic profiles.

477. Supposing these cannabis plant products are made available. In what form should they be made available?

A. That is very difficult. We now have the Home Office sponsored cannabis farm in Kent. I would assume that the best thing is to supply it as cannabis plant. I cannot imagine that, with our current knowledge, separating out naturally occurring cannabinoids would be all that useful because we would not really know how to use them. As far as I am aware, we only know about cannabidiol and Delta 9 THC. Delta 8 THC looks very interesting. I understand from a colleague that it is actually much easier to make and cheaper to make. That could be a very important way forward. I should have mentioned that the use in children of cannabinoids is extremely compelling, probably because of the lack of development of the CB1 receptor and therefore the lack of psychotropic effects in children, for example, who are vomiting. There is this single pilot study and it is incomprehensible to me why it has not been followed up, given the extremely positive result that was achieved there. It is astonishing.

478. You are suggesting that this field in Kent, where I have come from this morning, would just produce a cannabis plant, not an extract, and this would be legitimised?

A. My knowledge on this is limited to the small paragraph in *The Times*. I have absolutely no knowledge about it at all. It is probably just a smoke screen put in there to put us off the scent, but I would imagine that that could be the source of the compassionate reefer. Beyond that, I cannot imagine what it could provide.



16 June 1998]

DR PHILIP ROBSON

[Continued]

Lord Porter of Luddenham *contd.*]

479. It would not form a good basis for a rigorous research programme unless it was much more standardised?

A. I am far more emphasising the cannabis reefers, if you like, for this very limited use in medicine now. Obviously, the research that has to be done has to be on the cannabinoids. We have to understand the individual effects of the cannabinoids and how they interact with each other, but in a controlled way. I am quite sure that is right. It is not so much research on smoked cannabis I am interested in; it is access to it for patients who need it now.

480. My question was about future clinical trials. I think your answer is perhaps no, there is not a place.

A. You are forcing me to think on my feet, which is very good. I am sure there would be some scope for restricted clinical trials to justify what at the moment is a supposition. The supposition is that smoked cannabis is more effective, but is it just because of the route? I would at least like to examine that. I would like to compare, for example, smoked whole cannabis with smoked THC in MS patients perhaps, and there we come to the problem of outcome measures, but it would be very interesting and important to do that.

481. Is it the whole plant that you are recommending? Is that what you would like to see made available as well as nabilone?

A. For the compassionate reefer, yes. For this particular restricted area of establishing whether or not smoked cannabis is better than smoked THC, yes. Otherwise, no. I would hope that it would be the source for perhaps individual cannabinoids that cannot at the moment be synthesised.

*Lord Dixon-Smith*

482. Dr Robson, we come to this appalling problem of properly controlled experimental designs so that you get valid results, bearing in mind that your cannabis plants anyway contain 61 cannabinoids, as I understand it. Presumably, when you smoke cannabis, it is the combination that matters rather than the individuals. Of course, then you have a problem because this is a psychoactive agent and I imagine that judging results is made that much more difficult. What are the problems of doing this, bearing in mind that it must, it seems to me, be immensely complex, and, if you like, you always have the fallback of being able to go back to the natural plant which you could standardise by cloning and standardised production methods. It is a wonderfully fruitful field to experiment in and one could indulge enormous sums of money from somewhere. Is it all worthwhile?

A. The review of the literature, which is so tantalising, does suggest that it is worthwhile because these are substances which have a range of effects that are fascinating. What we do not need is any more piecemeal research. We need some sort of central coordination for the research. I think that should perhaps usefully include the ethical issue too. Obviously, any human research is going to have to be approved by an ethics committee, but I feel that it would be far better to have a sophisticated and carefully appointed central ethics committee which

would perhaps consider all applications to do human research in this area, which would be alongside the central coordinating function, perhaps based on something like the Royal Pharmaceutical Society or something of that sort, so that we do not have the frustrating experience ten years from now of having more tantalising hints but nothing that you can really confidently hang your hat on or, perhaps more importantly, that a pharmaceutical company can hang its hat on. If we had this central organisation and this energy two things I think would happen. First, cannabis would become a bit more respectable. I was talking to an obstetrician yesterday. One of the fascinating historical applications is in labour, preventing haemorrhage after labour, hurrying labour along and soothing pain in labour. This goes back 6,000 years. It is a robust indication but there is nothing since the 19th century that has been written on this. When I spoke to this professor of obstetrics, he said that there are definite gaps in modern obstetrics. Some patients are not suitable for epidurals. Some patients do have delayed labour. If you could have an agent which both speeded labour up, prevented haemorrhage after labour and reduced pain, this would be very desirable. Cannabis is so disreputable that nobody would begin to think of that and yet that is really an obvious application that we should seriously consider with perhaps some basic research and pursue it. The only way that is going to happen is if we have this central control and organisation. Following on from that would come the stimulation of interest of the pharmaceutical industry which is going to be central to the future development of cannabinoids. We do have a problem about the cost of dronabinol compared to the cheapness of the natural plant. This is a huge contrast and one which I have not any answers to. It is extraordinary. Perhaps some of the other cannabinoids that could be uncovered would be cheaper to make and I am hoping that is what will happen.

*Chairman*

483. The other part of the question is, who should organise and sponsor such a controlled and centralised effort?

A. I do not have any very clear, idea but it could easily be the Royal Pharmaceutical Society with a group of interested basic scientists and clinicians who have had experience both in the specifics of cannabinoids and also in the wider planning and carrying out of clinical research so as to get a theme. Every trial that is done, every piece of research that is done, has to have the stamp of approval, of quality control, from this central organisation so that, at the end of the five or ten year period, there will be a body of evidence that will convince people and not simply be a titbit. I feel that that sort of organisation could well attract the MRC and the Wellcome Trust and other major players in a way that they will not be attracted by perhaps individuals attempting in the wilderness trials, which are probably of a rather low quality simply because of the challenge that there is to an individual working on their own.

---

16 June 1998]

DR PHILIP ROBSON

[Continued

---

Chairman *contd.*]

484. I wonder whether the Royal Pharmaceutical Society would be appropriate or whether the British Pharmacological Society would be more appropriate?

A. Very possibly. I do not have any strong views on that, but I am sure that there should be a central

coordinating body. I think this business of the ethics really ought to be considered alongside it because it would be enormously helpful to have that consideration built into the research planning.

Chairman] Thank you very much indeed.

---



TUESDAY 30 JUNE 1998

Present:

Butterfield L.  
Butterworth L.  
Dixon-Smith L.  
Nathan L.

Perry of Walton L. (Chairman)  
Porter of Luddenham L.  
Rea L.  
Walton of Detchant L.

## Examination of Witnesses

DR JAN VAN AMSTERDAM and DR JAN WILLEM VAN DER LAAN, National Institute of Public Health and the Environment, The Netherlands, were examined.

Chairman

485. Thank you very much, gentlemen, for coming. We are most grateful to you. Could we start by asking you to introduce yourselves and explain your role in the National Institute for Public Health?

(*Dr van Amsterdam*) I am Jan van Amsterdam. I am an immunopharmacologist and I am working at the National Institute of Public Health. In part, I am doing research in the field of immunopharmacology and, in part, I take part in the registration of neuropharmaceuticals. I specialise in the CNS functions.

(*Dr van der Laan*) My Lord Chairman, for us it is a great honour to be here to explain our report<sup>1</sup> and to answer your questions. I am Jan Willem van der Laan, pharmacologist and toxicologist. From 1980 to 1990, I was head of the section on psychopharmacology. We did research on opiate dependents and benzodiazepine dependence. From 1990 onwards, I have been head of the preclinical assessment group of the Medicines Evaluation Board in The Netherlands.

486. How did you become interested in cannabis? What prompted the report?

(*Dr van der Laan*) As researchers, we remain active in this field, after changing our jobs somewhat. Our interests are in illicit drugs such as heroin, ecstasy and cannabis and because of the Pope's paper, published in 1995, the Inspectorate for Pharmaceuticals and Medical Technology asked for advice in 1996. Within six months, we were able to finish the literature survey as given in the report.

Lord Rea

487. In your report, one of the things that you explain is that there are methodological problems in assessing long-term effects of cannabis use. Could you go into some of these, explain them and describe why you feel that some published reports on cannabis suffer from these weaknesses?

(*Dr van Amsterdam*) It is indeed difficult to determine residual effects of cannabis for a number of reasons. First, it is a problem because cannabinoids are very slowly released and it requires

several days before the subjects are clean. You want to test subjects when they are clean, so you should take care of the non-washout of the subjects. It may need several days. In most studies, the research is done on maybe one or two days, but no more. That may be too short to have the subjects free of the cannabinoids. Secondly, it is difficult to estimate the dose because people are using cannabis over longer periods and you cannot control how large the dose was which they received in this long period. The third point is that it is practically impossible to perform laboratory studies to control the long term cannabis intake so you are dependent on naturalistic studies, from which you cannot control the polydrug use. Fourth, studying neuropsychological effects is cumbersome, mostly because you do not know the predose level. It is very difficult to match the cannabis using group with the controls. Two points remain to be mentioned. The abrupt disruption of heavy cannabis use might precipitate withdrawal syndrome, which might affect the test—loss of concentration, etc. Finally, a large proportion of the country's users are polydrug users. I am not talking about co-use of heroin but rather alcohol or, recently, ecstasy. Those are a number of points which hinder proper investigation of long term drug effects of cannabis<sup>2</sup>.

488. Do you think that many studies have not addressed these difficulties adequately and therefore can be held to be not definitive in their findings?

(*Dr van Amsterdam*) Partly they do, but mostly they do not. The investigators try to do their best. It is a very difficult point. You are going up to the limit, but most researchers do not take account of all the points I mentioned.

489. It helps if at least they acknowledge that these problems exist, rather than denying them. It helps, when presenting results of research, to at least delineate the problems before making interpretations.

(*Dr van Amsterdam*) Yes.

<sup>1</sup> *Residual cognitive and psychotic effects of prolonged heavy cannabis use*, by J G C van Amsterdam, J W van der Laan and J L Slangen. National Institute of Public Health and The Environment, October 1996, published in Dutch in *Ned. Tijdschr. Geneeskunde* 142 (10), 504-508, 1998.

<sup>2</sup> *Note from witness*: Reason 1 (slow washout) and reason 5 (withdrawal) would just lead to impaired performance of heavy cannabis users in cognitive tests (compared to control subjects). Still, only minor effects on cognitive functioning are observed, emphasising the conclusion that eventual residual cognitive effects are small and of little relevance.

30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued]

*Lord Porter of Luddenham*

490. In your report on the effects of prolonged heavy cannabis use, you very usefully define what you mean by this. You define prolonged heavy cannabis use as daily consumption for more than six months, but surely it depends on how much a day they take, does it not? Will it not cover a pretty wide range of daily doses of THC and is there any evidence that the effects which you describe are dose related?

(*Dr van Amsterdam*) The latter point is a very good point because, as a pharmacologist, it is important that the facts you know are dose dependent. First of all, we observed only very small effects on cognitive behaviour. The question of dose dependency is therefore very hard to prove for the reasons I mentioned before. It is very hard to define dose dependency and I cannot inform you about whether it has dose dependency or not because the effects were very small.

491. If they were very small effects which you cannot measure really on cognitive behaviour, what are we talking about? What are the effects?

(*Dr van Amsterdam*) That is a good point. We could not assess that there are effects. We reviewed the studies which took heavy cannabis users, so they have tried the highest dose possible and still you only see very small effects on cognitive behaviour, so we conclude that, when there are effects, they are very small.

492. We are told that people get stoned on cannabis.

(*Dr van Amsterdam*) They do.

493. That is surely a major effect, is it not?

(*Dr van der Laan*) You are asking for the type of effects. The studies on cognitive behaviour are carried out with a lot of psychological tests: card sorting, symbol sorting and other very simple tests, word remembering and so on. There are a lot of those types of tests and in all the publications we have looked at different types of tests, and sometimes similar types of test have been used. However, it was very difficult if there were effects in one study, and a certain test may be one out of five tests. In another study, another test on another aspect seemed to show an effect, so the studies were not consistent with respect to their different psychological effects on remembrance, sorting and small motor behaviour and so on.

494. If you cannot measure or even detect cognitive effects, what are the effects that we are talking about? What effects are there of cannabis which are not cognitive? I am not sure what we are worrying about if there are no effects. What are the effects that the smoker of cannabis detects and the reasons he smokes it?

(*Dr van Amsterdam*) In the acute situations, there are effects; he or she is stoned. What we studied was when you stop smoking and observe the individuals after, say, several days. You do not see any residual effects. When you have heavy use of cannabis or use for a longer period, you do not have irreversible effects on cognitive behaviour when you have stopped smoking. That is the point we want to make.

Lord Porter of Luddenham] You are particularly concerned with chronic effects, but you are not

concerned with the strong, acute effects of very heavy doses. It is the longer term that we are talking about.

*Lord Nathan*

495. We heard some evidence that there is marked variability in the chemical composition of cannabis, not only between countries where it is grown but between crops and indeed between plants. Is that a material factor in relation to your studies?

(*Dr van Amsterdam*) It hinders proper determination of the dose. When you compare Dutch users, who have good quality cannabis, with users in other countries, you have different doses. Some of them use flowers and some use other parts of the plant, so they have all different contents of THC. It is very difficult to establish dose, certainly in naturalistic studies, because you do not have any idea about the kind of cannabis used. That hinders and troubles the assessment of effects.

496. The assessment of dose, as was very fairly pointed out earlier, is not something which you have been into and controlled. Maybe it is very difficult or impossible to do so unless you can identify the exact quantity of cannabinoids and so forth in the particular cannabis plant.

(*Dr van Amsterdam*) You are quite right. When you cannot do a study under proper conditions, you have a very weak conclusion, but there are no other means to do these studies. This is the problem.

*Lord Butterfield*

497. I think we can all see how complicated it is but have you in your country any studies of cognitive changes when people are smoking cannabis or taking it in any way, not after they withdraw it for a little while, but while they are actually in the process of getting stoned? You have explained how, if you stop smoking cannabis, you do not have much of a problem with your mental activities, and we would be very interested to know if there are any studies in your country where people who have been smoking have been studied during the smoking period.

(*Dr van Amsterdam*) First of all, we reviewed worldwide literature so what we are talking about are not specifically Dutch studies. Secondly, we were not interested in the acute effects of cannabis. We were only interested in the residual effects after stopping long term cannabis use. I cannot inform you about the acute effects.

498. One of the things which has been interesting is the possibility that cannabis and cannabinoids, having moved into the adipose tissue, may come back into the blood. Have you reviewed any evidence that established levels of THC in the plasma due to leakage from fat stores can reach a pharmacologically effective range? Detection of very low levels of compounds is now widely possible with high levels of chromatology and resolution. Have you seen people taking cannabis and later having levels coming back into the blood during the withdrawal period which are pharmacologically active, or are they just traces?

(*Dr van Amsterdam*) That is a very difficult point. I have to disappoint you because we did not investigate these effects. Again, you are referring to



30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued

Lord Butterfield *contd.*]

the acute effects. It is quite possible that THC is released slowly from the adipose tissue and fat store deposits, but you are referring to the acute effects and we have not reviewed that.

*Chairman*

499. If you have six months' daily usage of cannabis, you are going to have a large amount of storage in the fat. It is going to take weeks, if not months, to eliminate this so it is certainly not an acute effect.

(*Dr van Amsterdam*) You are quite right, but in the beginning of our conversation I mentioned six points which are hindering the study of residual effects. One of my points was that the cannabinoids are very slowly released from fat stores. When you use a washout period which is not long enough, you have these kinds of problems in your studies, so you are in fact studying the acute effects of cannabis and not the residual effects of cannabis use.

*Lord Butterfield*

500. When I was younger, I was very intrigued about the circulation through the adipose tissue and how much it increased in hot weather. I wonder whether you have any evidence that this bringing back of cannabinoids into the circulation was more noticeable in hot weather?

(*Dr van Amsterdam*) I am sorry; I cannot help you.

(*Dr van der Laan*) May I try to give some comments? What you refer to would only occur in single cases. It would only be reported as a sudden event in people's lives. That is very difficult to pick up in scientific literature and to study it really. Maybe you are right that, in certain cases, maybe if people are hungry or starving, the adipose tissues are releasing more of the active substance in them. In those cases, there will be a flashback. We know from literature that the flashback in cannabis use is reported, but the incidence of this phenomenon is very difficult to detect.

Lord Butterfield] I understand. It would be marvellous if we could get into a state where we could do more clinical physiological experiments on cannabinoids. One which I would be very interested in following would be placing people who are heavy smokers in a heat chamber when they can get a good flush of blood through their adipose tissue to see if it affects them. You laugh, but there are heat waves: if a person has been smoking cannabis, there might be at greater risk, getting into a motor car when the weather is hot, than during a cold winter period when the circulation in the subcutaneous tissues is very low. I suppose you have not any evidence about the implications for cannabinoids coming back into the circulation affecting driving. I quite see that, to do it under clinical circumstances, you have to run around with a syringe while people are doing things and grab them at the moment when you think you would like to study them; whereas if you do clinical physiology you can put them in heat chambers and see what is happening.

*Lord Rea*

501. Are there any studies which show a rise in blood levels of THC during the run-down period? Is it a steady drop down or are there any instances where it rises sometimes during the follow-up period of somebody who is well over the acute psychoactive phase? Does it ever rise up to near psychoactive levels again, without further smoking?

(*Dr van Amsterdam*) I am not aware of these studies but that says nothing because we did not direct our studies to these kinds of details. We were aiming at the residual cognitive effects and we did not study in detail metabolism and release of THC from fat stores etc. I cannot be of any help; I am sorry.

*Chairman*

502. In your review of the literature, did it show how long after stopping each of the studies were made? You talk of residual effects. What do you mean by "residual"? You said that during the washout period that is not residual; that is still acute. How long did these studies go on?

(*Dr van Amsterdam*) It depended on the study. The old study used only washout periods of four hours. Later on, they used 24 hours, 18 hours or, one night, they were guarded in the hospital and the next morning they were tested. In our opinion, that is much too short because you have not washed out the cannabinoids, but there are one or two studies using 48 hours and these are, in my opinion, the best studies. There are only three or four very good studies which you can really use for your conclusion because the old studies were using too short washout periods. In these four studies using 24 hour to 48 hour washout, we observed only very mild effects on cognitive behaviour. That is what I call residual effect. The subjects did not use cannabis for a period of 24 hours to 48 hours. Then they were tested and compared with a control group which did not use cannabis. One of the problems was to match these two groups because both groups were using alcohol too.

*Lord Dixon-Smith*

503. Have you noticed any antimotivational effect as a result of heavy cannabis use? Is it in any way similar to the effect of either heavy alcohol abuse or heavy tobacco use? Is there a problem in identifying this anyway because some users—it is difficult to say what proportion—tend to come from sections of society which are not motivated in the first place.

(*Dr van Amsterdam*) In our opinion, there is no proof for amotivational syndrome, at least not as a residual effect. In the acute phase, you may expect that people are not motivated because they are stoned, so they do not like to do anything. They want to sit and smoke. As a residual effect of cannabis, we did not have any proof that there was an amotivational syndrome. Underlying depression was once mentioned as a cause of residual amotivational syndrome but I think you cannot include that.

(*Dr van der Laan*) There is a lot of debate in psychiatry about the reasons why some people use these types of drugs—alcohol, benzodiazepine



30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued]

Lord Dixon-Smith *contd.*]

hypnotics, opiates, cannabis. There are some epidemiological studies in the United States indicating that part of the underlying illness may be indicated to be a depression. I am not aware, as far as we have reviewed the literature, that such studies have been done in a cannabis using population. They are mainly done in an alcohol using population. Maybe I am not aware of all the literature on that, but because of its social aspects, cannabis use is always located in specific areas in society so is it related to a specific motivational group? That is a disturbing idea.

504. Are you aware of any studies that have been done specifically amongst cannabis users who have been using it all their lives and, let us say, are now over 50 years old? There is a great deal of evidence that most people use cannabis at a fairly young age and then stop. Is there any evidence anywhere or studies that have been done on people who have used it all their lives and does that have any effect which can be demonstrated?

(*Dr van Amsterdam*) I am recalling some studies done in Jamaica or in the Caribbean area because those people are using heavy doses for a lifetime. I am not aware and I cannot recall whether they assessed whether there was amotivational syndrome present in these groups. I cannot really answer your question.

505. If the studies exist, at least we can go and look for them.

(*Dr van Amsterdam*) Again, these are old studies so we have to take care about washout etc.

*Lord Walton of Detchant*

506. There is a good deal of persuasive evidence in your own report and in much of the evidence that we have received that people who have had long term heavy cannabis use do develop cognitive decline. We have heard a bit about that this morning already in your answers. Presumably, this cognitive decline in many such studies has been assessed by detailed psychometric testing, but have you any evidence to indicate in which psychological domain that decline mostly occurs, in verbal or performance skills, or in memory or in other aspects of the individual's psychological constitution?

(*Dr van Amsterdam*) What I observe is that people are testing in the whole range. They are doing anything and everything.

507. So it is global?

(*Dr van Amsterdam*) Yes.

508. It is global cognitive decline?

(*Dr van Amsterdam*) Yes.

509. If you were to assess it in numerical terms, how severe has that cognitive decline proved to be in individual cases? If you were looking, for instance, at the arithmetical assessments that may be the result of such psychological assessment, can you give us any percentage indication?

(*Dr van Amsterdam*) I have that with me.

510. If you have any information, perhaps you could let us have it at a later stage.

(*Dr van Amsterdam*) Sure. I cannot find it just now.<sup>3</sup>

511. It follows that we should ask you whether, in your experience and in your reading of the literature, there is any evidence that, after people stop taking or smoking cannabis, that intellectual cognitive decline recovers and, if so, have you any indication as to how long it takes; or are there individuals in whom it proves to be permanent?

(*Dr van Amsterdam*) Maybe I repeat myself when I say that we did not see very large effects. We saw only very mild effects as residual effects of heavy cannabis use. You are talking about recovering and I cannot imagine how you can recover from something which was not there.

512. We have had a lot of evidence about cannabis-induced psychosis and we are well aware that heavy consumption may result in a delusional and hallucinatory state. A number of psychiatrists have told us that they are aware of patients who have been diagnosed as being schizophrenic when they were not aware that the individual was smoking cannabis. The question again is whether that psychosis is reversible after stopping smoking and the second question is whether you believe that cannabis intoxication can ever induce long-lasting schizophrenia in a genetically susceptible individual.

(*Dr van der Laan*) The relation between cannabis use and schizophrenia is very complex, as you have indicated. Also, after publishing our report and making a publication in the Dutch medical literature, we have had some discussions with psychiatrists on that point but thus far all literature indicates that cannabis as such is not leading to psychosis or schizophrenia or long-lasting schizophrenia. That is always a very difficult hypothesis. In most cases, it is to be expected that those people who develop schizophrenia should also develop schizophrenia without cannabis. The drug has only revealed schizophrenia in people with an underlying psychopathology. It is clear in several studies that cannabis use negatively affects the cause of schizophrenia.

513. And that a temporary reversible psychosis resembling schizophrenia may result—in other words, with hallucinations and delusions—from heavy cannabis use?

(*Dr van der Laan*) Yes, but in most people not leading to a permanent schizophrenia.

Lord Walton of Detchant] No, but a temporary psychosis. The reason I ask is based on personal experience because, many years ago, when I was practising as a neurologist, I saw a medical student

<sup>3</sup> Note from witness: On a battery of tests (Iowa grammar school tests) heavy users (more than 7 joints per week during 6.2 years) scored 10 per cent worse in two tests of long term retrieval scores in Buschke's test, 60 per cent worse in verbal expression, and 75 per cent worse in two mathematical test. However, in 20 other cognitive tests no differences were observed between heavy cannabis users and controls. Secondly, this study suffered from lack of supervision during abstinence; and a relatively short abstinence period of 24 hrs. Thirdly, users were more likely to have abused other drugs. On urine testing at the time of study 10 per cent of the users showed cocaine or codeine. Finally, others have reported no effects in the Buschke test.



30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued]

Lord Walton of Detchant *contd.*]

who, unknown to anyone, was a heavy cannabis user who developed delusions and hallucinations and was diagnosed as a schizophrenic and was given high doses of chlorpromazine and in consequence developed irreversible tardive dyskinesia. This is just one of the experiences that colours one's attitude.

Lord Rea

514. In the summary of your report, you say also that others argue that schizophrenics consume cannabis to relieve the symptoms of their illness but, in so doing, do they actually exacerbate it or does it have beneficial behavioral effects?

(Dr van Amsterdam) That is what we in Holland call the question of the egg and chicken; which one comes first? There are some people who believe that cannabis relieves the symptoms of the disease, but others deny it. There are two possibilities. I cannot give you a conclusion about that.

Lord Porter of Luddenham

515. Can I ask whether most cannabis users in The Netherlands also use other drugs? Are they poly-drug users? If so, can you comment on the adverse effects of long term cannabis use in this context, in the presence of other drugs?

(Dr van der Laan) We have done some recent research and found some studies on the Internet, published on heavy drug abuse in the Amsterdam population. It was part of a study also trying to get a picture on other, smaller cities in The Netherlands, but only the data for Amsterdam were published. The prevalence of other drug use for, say, tobacco and alcohol is 70 to 90 per cent. That is also in the last three months. Some 200 people using cannabis more than 25 times—a selection of the population—have ever used in their lives cocaine, heroin, ecstasy and the total part of that amounts to 65 per cent. For the last three months, only ten per cent of the population used other drugs such as cocaine, ecstasy and so on. The lifetime prevalence is high, 50 per cent, but the actual prevalence is much lower. We have, as far as I am aware, no literature on this type of combinational toxicology. Combinational toxicology is very difficult, so we try to do it in science by making ever abstracting answers. I am not aware of studies on the long-term interaction between alcohol and cannabis.

516. Could I ask a related question about whether cannabis use is an entrée to the use of other drugs? Does it lead to the use of other drugs or does it do the opposite and keep people on a relatively safe drug like cannabis?

(Dr van der Laan) It depends on what is to be taken as a drug. If you look at alcohol and tobacco, I am pretty sure that most children are starting with that type and then after that they use cannabis. That depends on the political situation. There is a recent review by a specialist on the governmental service of public health in Amsterdam, indicating that a lot of people in The Netherlands are not fulfilling the stepping stone theory that you refer to, of using cannabis as a first step, going in each case to other drugs such as heroin and cocaine.

517. That does not happen?

(Dr van der Laan) No. We try, at least in The Netherlands, to separate that area, also, by the way, the police are acting in these problems.

Lord Walton of Detchant

518. Are the outlets through which cannabis is available the same as the outlets through which other drugs are available, such as heroin and cocaine?

(Dr van Amsterdam) In Holland?

519. Yes.

(Dr van Amsterdam) Certainly not, no. The penalties for heroin use and trade are increasing while the penalties for cannabis have decreased. In the so-called coffee shops, which is a familiar term now on the Internet, you can only buy cannabis, but very seldom other drugs. They want to prohibit the selling of alcohol in these coffee shops. Use and trade in heroin is not allowed at all in Holland.

Lord Porter of Luddenham

520. What is the trend in Holland in cannabis use and heavy drug use? Are they both going up or is one going up and the other coming down? What is the trend over the last ten years or so?

(Dr van Amsterdam) As far as I recall, the problem of heroin in Holland is negligible. These subjects are very old and they will die when they are 50 or 60 like normal people do, but they are not increasing. The number of heroin addicts is not increasing in Holland. On the other hand, the number of cannabis users is increasing as well as are the subjects who are trying ecstasy, which is the new trend.

Lord Nathan

521. You touched on the question of the source of supply of cannabis. I wonder whether you could guide us as to what the legal position in Holland is, not in detail but in outline, as to the possession of cannabis? You speak of the coffee shops. Perhaps you could guide us. Is there any prohibition on the coffee shops supplying it and, if so, where do they get it from? Is there a problem with regard to the promotion of cannabis consumption in the same way as the large tobacco companies used to promote tobacco consumption very strongly? Could you give us a general picture?

(Dr van Amsterdam) In Holland, we have the problem of the front door and back door. At the front door, you can buy as a consumer of cannabis but the government does not allow the owners of the coffee shops to buy the cannabis in from their suppliers at the back door. They have to buy in cannabis at their back door illegally, and sell it officially at the front door, which is allowed.

522. [Unallocated]

523. [Unallocated]

524. [Unallocated]

30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued

*Lord Dixon-Smith*

525. Do you have any information as to how they actually do this? If they are allowed to sell it but they are not allowed to buy it, that is nonsense.

(*Dr van der Laan*) You have to be aware that we are workers for the government so that is a problem of justice and the police and we do not have that full information. That is how it is going. Just last week, a boat with 13 tons of marijuana was picked up from Morocco, going to Spain and Gibraltar. The big boys will be punished. The formal policy in The Netherlands—and I think you are fully aware of it—is to try to catch the big boys and not the small ones.

*Lord Porter of Luddenham*

526. Legally, you are allowed to sell in the coffee shop but you are not allowed to buy.

(*Dr van der Laan*) Legally, you are not punished. You are not allowed but you are not punished.

*Lord Dixon-Smith*

527. The law says that it is not legal but the law will not pursue an individual who is only dealing in small quantities?

(*Dr van der Laan*) The problem is if the law should be maintained at that level. There are no personnel for other areas in justice.

*Lord Porter of Luddenham*

528. Are you aware of the policy which has been recommended recently by *The Lancet*, the British medical journal? It sounds to me very much on the same lines.

(*Dr van Amsterdam*) It is advocated by other countries too. Recently, there was a report by the French Institute of Health in which it was claimed that the danger of alcohol was much larger than the dangers of cannabis. There are some differences between the official policy of the French Government and what their governmental institutes are producing.

*Lord Rea*

529. Are there voices in Holland advocating that the state should actually buy supplies of cannabis and officially distribute them to these coffee shops, thereby being able to take a fair amount of tax at the same time?

(*Dr van Amsterdam*) This is a problem because the tax officers visit the growing houses for cannabis and they do not tell the police because for them the most important thing is that those who are growing the cannabis are paying their taxes on the cannabis. The real Dutch people are always interested in money.

*Lord Dixon-Smith*

530. What is the attitude to cultivating cannabis in Holland? Is it illegal?

(*Dr van Amsterdam*) It is illegal.

531. Do the coffee shops have a large tropical glass house at the back, in which they are growing their own supplies?

(*Dr van Amsterdam*) That is the problem. It is illegal to grow cannabis. It is only legal to possess some minor quantities of cannabis for everybody.

*Chairman*

532. How addictive do you think cannabis is from the reviews that you have done? How strong is the evidence for people becoming addicted to cannabis?

(*Dr van der Laan*) The problem of addiction is always in the literature, comparing opiates and other drugs. The addiction to cannabis is much less comparing it with opiates. One important thing is the long half life, the slow elimination of cannabinoids, leading in itself to a slow restoration of the physiology. This in itself is an intrinsic protection against withdrawal. There are some reports about withdrawal symptoms. They are not very consistent but they are also very old. I have some references from 1934 and 1944. The most important symptoms are irritability, outbursts of excitement, violence and so on, but this depends also on the character of the person. There is also injection of animals which is fairly productive for the abuse potential of drugs. It is not consistent to induce self-administration in monkeys in a certain state. Two out of six indicated that the self-administration potential of cannabis is lower than opiates and amphetamines.

533. Are you continuing to review the cannabis literature? Have you continued to review since the report was published and are there any significant new findings since then?

(*Dr van Amsterdam*) We have not written another report. We are following the literature but we do not note any important developments in this field.

534. Are there any other points you would like to comment on?

(*Dr van der Laan*) Yes. From the report, it is possible that you get the impression that we would stimulate the use of cannabis. That is not our purpose. Just as the public fight against tobacco use because of the induction of lung cancer, also for cannabis smoking there is an increase in cancer in the head and neck region. That is also an important element at the same level as for tobacco. The acute effects are also important to note. If it is deteriorating the social function in classrooms and so on, we should be aware of that and we should not use it during school time. These are elements that we should keep in mind if we discuss cannabis. One argument is that very long use of alcohol has strong effects on the liver. That type of effect is not known for cannabis. We could not find it.

535. If people use cannabis for long enough, you will get comparable figures.

(*Dr van Amsterdam*) That is correct.

*Lord Porter of Luddenham*

536. In the coffee shops, is the cannabis always sold as a smoking mixture or can you buy it to put in foods or as resin?

(*Dr van Amsterdam*) You can buy it in small plastic bags and then you can mix it with normal tobacco,



30 June 1998]

DR JAN VAN AMSTERDAM AND DR JAN WILLEM VAN DER LAAN

[Continued]

Lord Porter of Luddenham *contd.*]

which many people do, or you can take it home and bake a cake, whatever you like.

537. But it is just a weed?

(*Dr van Amsterdam*) Yes.

*Lord Walton of Detchant*

538. Is there a strong movement in The Netherlands for cannabis to be made legal?

(*Dr van der Laan*) As a reaction to our report and our publication in the medical literature, there were two people from the second chamber of Parliament, one indicating that the report was bad; it was not possible to give cannabis free and one from the other side, the Liberal Democrats, indicating yes; we have always said it should be free. Both those types of reaction are in Parliament.

*Lord Butterfield*

539. Who might be able to tell us where the decision is made that a person is a big dealer? Are there reports each year from the people who are concerned with importations about how they are trying to locate the people who are sending cannabis in large quantities into your country? Do your Customs officers produce annual reports which might give us a clue?

(*Dr van Amsterdam*) They do. They are producing annual reports referring to confiscating cannabis and these are available.

540. Presumably, the number of people working in the Customs services may be increasing in the attempt to find the loopholes in the importation of drugs, including cannabis, or is that not true? Suppose the Customs people were entirely successful. Is enough cannabis being grown locally in The Netherlands to satisfy the coffee shops?

(*Dr van der Laan*) One of the possibilities, if you have a front door and a back door, is allowing the coffee shops to buy their cannabis somewhere and to follow the bigger guys behind the door. In that way, the police are working to find the big boys and also to find the big storages. That is the problem we have. If we put all coffee shop owners in prison, the prison would be full, but the people who make the real money are in the street. We try to do it in another way. Regularly in the daily journals there are messages that huge amounts of cannabis are picked up from the harbour in Rotterdam or from some plants somewhere in the country which are not allowed. There is an active policy against the big boys.

*Lord Rea*

541. It must be a fine balance because if they are too successful in picking up the big boys then the coffee shops will have no cannabis.

(*Dr van der Laan*) That is so.

Chairman] Thank you very much indeed for coming and answering our questions.

#### Letter from Dr van Amsterdam

First of all I cordially thank the Committee for the pleasant discussion we had yesterday on cannabis. In response to the questions raised concerning the Dutch cannabis policy and consumption, I contacted the Trimbos Institute here in Utrecht for further information.

Mrs Dr Inge Spruit told me that cannabis consumption is increasing in The Netherlands just like it does in other European countries. The introduction of the so-called coffee shops which is a *de facto* legalisation did not alter this increasing trend (no stimulus of cannabis consumption by coffee shops).

For your further information I enclose some additional information on cannabis in The Netherlands.

If you have additional questions, please contact Dr Spruit who is an expert in the field of epidemiology of cannabis use.

*Dr J G C van Amsterdam*

1 July 1998

---

TUESDAY 14 JULY 1998

---

Present:

|                                |                               |
|--------------------------------|-------------------------------|
| Butterworth, L.                | Porter of Luddenham, L.       |
| Dixon-Smith, L.                | Rea, L.                       |
| Kirkwood, L.                   | Soulsby of Swaffham Prior, L. |
| Perry of Walton, L. (Chairman) |                               |

---

**Memorandum by Mr Neil Montgomery, University of Edinburgh****PURITY AND DOSAGE IN THE RECREATIONAL AND THERAPEUTIC USE OF CANNABIS****1. INTRODUCTION**

1.1 In assessing issues of “purity and dosage” I will separate cannabis users in the UK into four distinct groups, three of which apply to recreational use (Casual, Regular and Heavy users) and one to therapeutic use. Certain notable aspects, particularly those of purity, will be pertinent to all four groups while others, mainly related to dosage, will be specific to each group. Let me begin by describing the four groups:

1.2 The Casual user is one who indulges in cannabis for recreational purposes on an irregular basis, consuming no more than one ounce of cannabis resin (28.4 grams) in any one year. They require very little cannabis—less than 0.1 grams—to become “stoned”; that is, to experience the drug’s psychoactive effects<sup>i</sup>. They may consume up to one gram over a six-hour period, remaining “stoned” but still functioning; however, the consumption of any more than one gram, within such a period, will inevitably cause the user to “whities”; a disturbing episode of nausea, dizziness, immobility and general unpleasantness which will last anywhere between a few minutes to an hour.

1.3 The Regular user exemplifies the average cannabis user in the UK and will consume, for recreational purposes, one eighth of an ounce (3.5 grams) of cannabis resin<sup>ii</sup> per week. They usually<sup>iii</sup> require more than half a gram to become “stoned” but after 0.1 grams will begin to feel a mild psychoactive effect which they will maintain throughout, most commonly, an evening’s consumption. The Regular user may consume cannabis throughout the day, whether they are working or not<sup>iv</sup>. Having experienced “whities” in the past, they will regulate their consumption to avoid the experience again. Most experienced Regular users—those who have been using cannabis for more than two years—are likely to have gaps of several years between “whities”; perhaps only experiencing a few “whities” in their life.

1.4 The Heavy user is in a minority<sup>v</sup> among recreational cannabis users, consuming up to and beyond one ounce (28.4 grams) of cannabis resin per week. These are people who have become dependent on cannabis; they are psychologically<sup>vi</sup> addicted to the almost constant consumption of cannabis. The Heavy user will consume more than the Regular user’s weekly amount in one day; more than one eighth of an ounce (3.5 grams). Becoming “stoned” and remaining “stoned” throughout the day is their prime directive. A heavy user would need to consume a considerable amount of cannabis, at least one quarter of an ounce (7 grams), within a short period of time (perhaps two hours) before encountering the “whities” experience; if at all.

1.5 The Therapeutic user belongs to a group which is formed from a complex mixture of recreational and non-recreational users suffering from a wide range of ailments that appear to demand various levels of dosage which relate to both their experience with cannabis as a recreational drug and their therapeutic needs. An increasing trend within this group is to abandon the illicit market and grow their own cannabis at home<sup>vii</sup>; primarily, to avoid problems of impurity.

**2. PURITY**

2.1 There has been no scientific survey of the purity of cannabis resin being consumed in the UK<sup>viii</sup>. The most common form of cannabis used in the UK is imported cannabis resin and there are two specific causes of its contamination: (a) substances, like boot polish, treacle, wax, henna, soil and glue are added to cannabis resin before importation to increase its weight, thus artificially increasing its value; (b) blocks of cannabis resin may be secreted for importation in petrol tanks, immersed in diesel, or packed closely with other particularly pungent substances to disguise its own distinct aroma and thus is contaminated through absorption. To properly assess health risks associated with the consumption of cannabis resin within the UK it is absolutely crucial that we have a clearer picture of what exactly is being consumed along with the cannabis.

2.2 Quality control is not completely non-existent because the market tends to regulate itself (nobody wants to buy a substandard product) however, the control only extends to that which is so obviously contaminated that it is not sellable. There are no guidelines, regulations or inspections to maintain control over the quality of a substance which is being consumed by a sizable minority of the population (7.5 million)<sup>ix</sup>.



*14 July 1998]**[Continued]*

Control over the quality of products in an illicit market cannot be maintained. The argument for proper quality control is an obvious one when we discuss cannabis as a therapeutic agent (it is inconceivable that the medical profession would proceed on any other basis); the consequences of extending such control become a serious and complex issue if we want to be equally concerned about the health of recreational users.

2.3 The purity of cannabis resin and potency of different types of cannabis (resin or herbal) have direct links to dosage. For those who are applying self-medication, purity is of paramount importance; they are depending on an effect for some form of relief and are likely to consume more “contaminated” product than their usual dose in an attempt to find that relief. Of course when they next acquire cannabis of a higher quality the processes for measuring out dosage remain the same, at least for the first application. Over-dosage, of this unintentional nature, is likely to cause distress and disruption to daily activity. The result is that the therapeutic user makes attempts at ensuring a continuity of supply either by buying cannabis resin in bulk or by growing their own at home; both activities—the possession of “more than what might be considered compatible with personal use” and “cultivation”—are serious crimes that may well result in a custodial sentence.

### 3. DOSAGE

3.1 The measurement of dosage for the therapeutic and recreational user is a process performed completely by eye and experience. There are a few people who will invest in expensive “gram scales” (weighing to within one hundredth of a gram) and laboriously subdivide their purchased cannabis into experientially discovered doses, but by far the most common processes lack any kind of accuracy or consistency.

3.2 Consistency of dose, however, is effected more by variations in the type of cannabis and potency than by the lack of accurate measurement systems, purity problems or the development of tolerance. Each type of cannabis has a unique psychological and physiological effect; for instance, a dark, malleable, Nepalese hash will produce a “stone” that swamps the entire body inducing a feeling of extreme heaviness and sluggishness, combined with a dulling of the general senses but tending to focus the mind, concentrating it on one process, one input; whereas, a Thai grass will produce only a slight physiological effect of light relaxation, general senses become alert and will be stimulated by minor changes in surroundings, a feeling of brightness, happiness and contentment will often lead to inexplicable giggling. This startling range of effects offers the recreational user desirable variety but can confuse and distress an inexperienced therapeutic user, perhaps not offering them the relief they expect.

3.3 The examples I have chosen are of course extremes, between which there is a complex mixture of effects; one further example to offer is Durban Poison, a grass which produces an effect similar to Nepalese Black for about fifteen or twenty minutes then the “stone” changes to a light, “speedy” effect similar in many ways to a Thai grass.

3.4 As if this were not complicated enough, the effect which one might expect from any one type of cannabis will itself be affected by the mood and actions of the user. If the user is in a mood to relax then they will be assisted; a sense of relaxation will be emphasised—depending on dosage the results can be gently calming or soporific—or, if the user is busy, has things to do, the same type of cannabis will stimulate action, keep them going and concentrate the mind. Because of this particular trait of cannabis I have found it difficult to describe it as a stimulant, or a depressant, or an intoxicant, or a euphoriant; it seems to be able to effect all senses in different ways. I thus suggest that a new description be applied which is less misleading than the others—sensoriant. As a sensoriant, cannabis is quite remarkably flexible with a potential for a broad range of uses and applications as a therapeutic; however, given its obvious complexity, much more research than is currently being conducted needs to be devoted to establishing what components, or more likely, what combinations of components within cannabis are responsible for each notable effect.

3.5 The two principle methods of consumption, eating and smoking, offer slightly different psychoactive effects and very different effect progressions; for the recreational user this is no more than a matter of choice but the differences appear to be very important to the therapeutic user<sup>x</sup>. Again, what I offer are two extremes in the scale of needs and applications: The therapeutic user who suffers from chronic pain can be relieved and satisfied through ingestion of solid matter by mouth—often cooked or melted into foodstuffs—however, the Multiple Sclerosis (MS) sufferer who aims to relieve involuntary spasms gains no satisfaction from eating cannabis because after consumption it takes anything up to two hours for the effect to begin; an MS sufferer cannot plan their spasms hours in advance. What the MS sufferer requires is a quick acting palliative, therefore they tend to smoke cannabis rather than eat it. When cannabis smoke is inhaled the effect begins within five seconds.

3.6 Difference in dosage are also apparent in these examples; “chronic pain” seems to require regular, large amounts of cannabis, leading this type of user to consume almost as much as a Heavy recreational user (up to five grams per day); “involuntary spasms” require only a small amount, commonly half a “joint” (approximately 0.1 grams), at the first indication of an impending attack.

3.7 There also appear to be considerable differences in the type of palliative effect in these two different conditions I have exemplified; the users with “chronic pain” say that the cannabis does not really take the pain away but makes the pain more bearable; whereas, users with MS experience a direct, identifiable intervention on their condition.

*14 July 1998]**[Continued]*

#### 4. TOLERANCE

4.1 A considerable tolerance is built up when cannabis is consumed on a regular basis; meaning that a heavy user requires at least eight times as much cannabis as a regular user to achieve the same effect. A regular user, too, is affected by a build up of tolerance in that while maintaining their standard dose they will not experience a powerful “stone” in the way that a casual user might. Quantifying this tolerance is likely to be a difficult task because of the variables noted above: a tolerance built up for one type of cannabis will not necessarily remain affective on the consumption of a different type of cannabis. Tolerance itself, however, seems not to be affected by mood and is not irreversible since a short break of at least two weeks, probably several months for a heavy user, will return them to a mimetic of the casual user.

4.2 As tolerance increases, the user will not appear to be, or feel, “stoned”. Thus regular or heavy users will be able to consume (usually smoke) cannabis throughout their working day without notice.

#### 5. CONCLUSION

5.1 If clinical trials are to be conducted, the variables noted must be taken into account either to standardise for accuracy in comparative studies or to extend the scope of individual research projects beyond one type of cannabis.

5.2 I believe, based on anthropological evidence, that there is a need for more research into the potential for effective therapeutics within the multifarious properties of cannabis, and that that research should be extended to illuminate consequences for the recreational user.

5.3 Further consideration needs to be given to methods of preparation and administration to satisfy the very different needs of the variously ill; and, to avoid the further complications associated with smoking while attending to its benefit of immediacy.

5.4 There seems no doubt that if the market in cannabis is to remain an illicit one then, if for no reason other than education, a clearer understanding of what impurities appear in cannabis resin used in the UK is essential.

5.5 I have found through my work as an Expert Witness<sup>xi</sup> in the field of cannabis use that the extent to which a heavy user can consume cannabis is largely unappreciated. In line with appreciating how little an amount is necessary for some therapeutic applications, further research into dosage for both recreational and therapeutic users should be conducted.

#### 6. EXPERIENCE

6.1 I have researched cannabis use since 1989. In 1994 I was commissioned by Channel Four Television to research the use of cannabis in the UK. My report resulted in their transmission of “Pot Night” (a series of cannabis related programmes); two articles of mine were published in their accompanying booklet and for “Pot Night” I produced a film entitled “Amsterdam by Night” which looks at cannabis culture and “coffee shop” society in Amsterdam. I am currently completing an MSc in Social Anthropology at Edinburgh University and will begin a PhD this autumn; my subject being cannabis. I am a Fellow of the Royal Society of Arts, a Fellow of the Royal Anthropological Institute and a member of the International Cannabinoid Research Society.

*12 May 1998*

#### NOTES

(i) See the section on Dosage for more information about the psychoactive effects of cannabis.

(ii) I will, in the main, refer to the use of cannabis resin (Hash) rather than herbal cannabis (Grass) since Hash is by far the most common form of cannabis in use, in the UK, today. It is, however, worth noting here that herbal cannabis is consumed at twice the rate (by weight) of cannabis resin.

(iii) This quantity will vary depending on the purity and type of cannabis being consumed; as will all the quantities referred to in this paper, unless otherwise specified, they are particular to the consumption of the most common varieties of cannabis resin that find their way to the UK and occupy the bulk of the illicit market—Dark Moroccan Hash; known as “Dark Rocky” or “Soap Bar”.

(iv) See the section on Psychological Effects for more information about dosage throughout the day.

(v) Heavy users form approximately 5 per cent of all recreational users in the UK—it could be considered that their use has gone beyond recreation to dependency but for now they will remain categorised as “recreational users”.

(vi) I say “psychologically addicted” because there appear to be no physical problems associated with stopping, even for the heavy user. There will, however, be a noticeable change in sleep patterns; the sleeping experience appears to be lighter and briefer during the first week after discontinuing use.

(vii) The last five years have shown a gradual increase in the home cultivation of cannabis in general but those with therapeutic stimulus seem more prepared to run the legal gauntlet than the casual or regular user.



14 July 1998]

[Continued

(viii) I have outlined a research project to the Scottish Office, Chief Scientist's Office which combines Anthropology and Forensic Science to tackle this very issue.

(ix) I have applied this figure using data from the ISDD research publication, "*Drug Misuse in Britain 1996*", 1997, p38, which covers only England and Wales; I have estimated an increase to include Scotland.

(x) For the moment I put aside any reluctance to smoke; however I make note of it in my conclusions.

(xi) I have provided Expert Evidence on 87 occasions to the High Courts and Sheriff Courts of Scotland and to the Crown Courts of England in cannabis cases; predominantly but not exclusively those that involve cultivation.

### Examination of Witness

MR NEIL MONTGOMERY, University of Edinburgh, was called in and examined.

*Chairman*

542. Good morning and thank you for coming. Could you tell us a little about yourself and how you came to be interested in studying cannabis?

(*Mr Montgomery*) Yes. My name is Neil Montgomery. I am currently a social anthropologist studying at post-graduate level with Edinburgh University's Department of Social Anthropology. I began studying cannabis in 1988 as a research project for Equinox, the Channel Four programme. This was into the therapeutic benefits of cannabis which at the time were not terribly well publicised. Through that research I was further commissioned by Channel Four to look into the use of cannabis in the United Kingdom. That research went on for 18 months and I produced a report entitled "Cannabis Sativa" which they then used to commission and transmit a series of programmes called "Pot Night" in March 1995. Following the research I had done for Channel Four I began to be asked by defence lawyers to appear in the Sheriff Courts and High Courts, and Crown Courts as an expert witness relaying my information about cannabis to the courts. I felt that if this were to happen more than once I ought to try and gain some authority for my research and proposed doctoral research at the Department of Social Anthropology. I chose social anthropology because there seemed to be very little anthropological research into the use of cannabis, although some anthropologists had commented on it. Edinburgh University accepted my proposal and I am now finishing their MSc introduction to the PhD which I will begin this autumn.

543. In your written evidence you provided some detailed information about cannabis use. Can you explain how you got it and how you undertook your study in the field?

A. My research is conducted in a traditional style of anthropology through participant observation over a long period of time, which means I become involved with cannabis users in their daily activities. I try and make contact with a broad range of cannabis users, including heavy users, what are called casual users and regular users, also therapeutic users of cannabis. I prefer silent observation but at times I become involved in their various procedures from the cultivation of cannabis through the selling and purchasing of cannabis, the communal consuming of cannabis and the use of cannabis for therapeutic purposes; so an intimate relationship has built up with around 500 informants over the past four or five years. I have tried to focus my research on 50

different specific informants for whom I am building life histories of their introduction to cannabis, the way that their cannabis use has developed throughout their life and the current status of their cannabis use. That work I hope to continue throughout my PhD and beyond.

544. You describe four different groups of cannabis users. Do you know approximately what proportion falls into each of these categories?

A. It is very difficult for me to say. I can take a guess at it. My estimate would be five per cent who could be considered heavy users, 30 per cent who could be considered regular users, a further five per cent who could be considered therapeutic users, the remaining 60 per cent being casual users.

545. I notice in your definition of the user there are big gaps between the amount that you suggest is typical of a casual user and the amount typical of a regular user. I presume that these are averages and that they are spread right through, or is there a dichotomy?

A. There tends to be a separation of sorts. I would not say there was a grey scale running from regular use to casual use. It seems to be that casual users will experiment with cannabis time and time again almost in a sense of having forgotten what it was like before and re-enter the use of it, sometimes just for one night. Sometimes maybe over a period of three or four weeks they will consume less than an eighth of an ounce and then they will stop again and re-try cannabis on another occasion. These people will rarely buy their own cannabis but will use cannabis when it has been offered to them; in various circumstances, usually parties or other recreational activities.

*Lord Porter of Luddenham*

546. In this respect it is very different from tobacco, is it not? I mean, there are not many casual users of tobacco. If they smoke, they smoke 20 a day or they are a heavy user.

A. Indeed, yes.

547. So there must be some difference. It is less addictive, I suppose, in some ways.

A. It would seem to be. My understanding is that cannabis is not physically addictive. However, heavy users demonstrate a dependency so I would consider that there was some kind of psychological addiction and perhaps the difference in types of addiction is why someone can be a casual user of cannabis.

14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Porter of Luddenham *contd.*]

548. Compared with cigarette smoking where a regular user I suppose might be smoking something like 20 a day, a heavy user might be smoking something like twice that many, how many smokes does the regular cannabis user use? It would not be 20 a day, would it?

A. I try not to use joints or reefers as an indicator of how much somebody is smoking, and I can perhaps tell you why later, but a regular user in this country tends to consume about an eighth of an ounce of cannabis resin per week or a quarter of an ounce of herbal cannabis, which would appear to be consumed at twice the rate of cannabis resin.

549. Just to help us, how many smokes would that mean? Would it be once a day or once a week?

A. That would be every day.

550. Once a day.

A. And it will be perhaps three or four smokes of a joint or a pipe usually in the evening.

551. Every day?

A. Every day.

552. And that is a regular user?

A. That is a regular user.

Lord Kirkwood

553. This pattern amongst users of having a period of taking cannabis for a month and then stopping does seem to be a strange pattern. Why do you think they stop? Is it a "whitey" that occurs or what?

A. Yes. This would be the casual user. My feeling is, and I am not a hundred per cent sure, that they do not particularly like cannabis as a recreational drug. However, they find it interesting and it makes a change for them as something alternative to alcohol, but they do not have the same interest in the effects that someone who is a regular user has, so they decide that they will not take it rather than being put off it.

Lord Soulsby of Swaffham Prior

554. In your explanation of who uses it: five per cent heavy users, 30 per cent regular, the word "misuse" has come into our lexicon in this enquiry. Where in that list would you put misuse? Where would it start? Not the legal side: I am talking about the medical use now. Where on that list would you put misuse?

A. Certainly with heavy users because the use of it disturbs their normal activities. They cannot conduct an ordinary life with their heavy use, which will begin first thing in the morning. They will roll a joint the night before to be ready for them when they waken up and they will continue smoking throughout the day, consuming an ounce or more of the resin in a week. That might cost them a hundred pounds a week, so they also have to take into account how that is affecting them financially as well as behaviourally. I think there may be some regular users who misuse the drug. I cannot identify how they might particularly misuse it, other than that they might become involved in petty crimes in order to obtain the cannabis that they use.

555. But is there a medical definition of misuse as well as the social definition which you are giving us?

A. I do not know that I could identify a medical definition of misuse.

556. Or is all use misuse?

A. That is a very difficult question. I would say not. It is at the moment because it is illegal.

557. Yes, we understand that.

A. If it were not illegal then perhaps it would not be misuse until it became a heavy amount of use.

Chairman

558. Could I ask whether you would consider the use of tobacco and alcohol were a misuse or use? It is the same thing.

A. Certainly alcohol.

Lord Dixon-Smith] We have talked about the percentage of users of cannabis, who fall into various categories. That misses what I would call the fifth user who is actually the non-user, so really my first question is: what proportion by your observations of society at large would you suppose is actually using cannabis?

Lord Butterworth] At all?

Lord Dixon-Smith

559. At all. That is the first question. Then, when you were discussing the casual users, you said that perhaps they were casual users because they were not interested in the effects of cannabis and that provoked a question in my mind of whether their lack of interest in the effects of cannabis actually altered the effects of cannabis on them. I do not know whether that is an observable fact.

A. First, the Government figures that were produced in 1996 for cannabis use compiled by the ISDD suggested 6.9 million cannabis users in the United Kingdom. I have increased that to 7.5 million to include Scotland because it was only England and Wales that was included in the survey. I do not think they are far wrong actually. I think that is a pretty fair estimation, although things could have developed in the past two years to increase those figures. On the other point, it would appear that some people using cannabis for the first time, even the first half a dozen times, will get very little effect indeed. I think this is because they expect something dramatic. They expect a psychedelic experience and they expect something that is hallucinogenic. When the effect that they receive from a couple of draws from a joint is very mild indeed, they feel that this is doing nothing for them and therefore not worth pursuing. Because they are leaving considerable gaps between each use of the drug, they are not building up any kind of tolerance or any understanding within themselves of what the drug is doing to them. Therefore, they are regularly expecting much more than they will get and this tends to put them off. Some people who have experienced the drug and perhaps consumed too much will experience the "whitey" that was referred to and not want to go back to using the drug. A "Whitey" is a particularly uncomfortable experience.



14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Dixon-Smith *contd.*]

560. Is there a distinction between if you like the effect of heavy cannabis use in Britain and heavy cannabis use in peoples in other parts of the world that is noticeable? Also, of course, although you have already touched on this, what particular adverse effects do heavy users experience?

A. I do not think there is a great difference between heavy use in this country and the experiences of someone who is a heavy user in another country. That is hopefully going to be part of my doctoral research where I would like to do a cross-cultural study between cannabis use in this country and cannabis use in East Central Africa. The pygmies in the Ituri Forest are considerable cannabis smokers and have been for generations and probably thousands of years. They rather interestingly demonstrate the same range of opinion about cannabis within their society, so there will be a small number of people who are very interested in, almost devoted to, cannabis use, and there will be some people who do not like it at all, and a range in between. What I would like to do is try and investigate how similar their gradation of use is to ours. I suspect it will not be too different.

Chairman

561. In your experience of the casual users and the regular users, are they mostly also using tobacco and alcohol at the same parties?

A. Mostly, yes. There is a tendency for the heavy user not to use alcohol. Probably, apart from anything else, they could not afford to do both. The majority of them are not likely to have that kind of income. The regular user who avoids alcohol tends to do so specifically. They make a very definite decision to avoid using alcohol. Other studies, particularly in the States, have shown that in the 11 states that decriminalised there was a shift of about 10 per cent away from alcohol towards cannabis which was very similar to the increase in cannabis users, so in some sense perhaps all drug use, if you link cannabis and alcohol, remained relatively stable but there was a shift from one over to the other. The other factor within it is that to combine cannabis and alcohol is not a terribly good idea. It tends to make the "whitey" much more of a possibility.

Lord Dixon-Smith

562. When we are discussing users can we assume that users come from all strata of society in relatively similar proportions?

A. Broadly speaking, yes. There is a tendency for perhaps poorer people to become heavy users. Interestingly, it would seem to help them cope with poverty better. This is something that was identified in the Indian Hemp Drug Commission report in 1895 as one of the identifiable sections of society who were using cannabis and these were the poor, who found it more acceptable to have some cannabis and no money than very little money and no cannabis.

Chairman

563. What proportion who smoke cannabis mixed it with tobacco?

A. Again it is very difficult to suggest what percentage might be involved here but I think the majority of cannabis smokers will smoke with tobacco. There has been an increase in the cultivation of cannabis at home. Some people will use herbal cannabis only. Even those who are growing at home will use herbal cannabis and tobacco mixed if they prefer to roll joints rather than use it in a pipe. Then almost everyone who is using cannabis resin, and that is by far the majority, will use it with tobacco.

Lord Porter of Luddenham

564. You told us that to some extent anyway, I think about 10 per cent, cannabis is an alternative to alcohol for people.

A. Yes.

565. Is this true also of nicotine?

A. I do not think so. In some respects I have noticed that the consumption of alcohol promotes the consumption of nicotine in that people who are in the pub drinking tend to smoke much more heavily than if they were not drinking. I am not entirely sure that tobacco consumption can be identified as a recreation in the same way that alcohol and cannabis can be.

Lord Soulsby of Swaffham Priory

566. Is there a tendency to progress from casual to regular to heavy use? You have described heavy users as addicted, but would this not also apply to casual users too or regular users, of being addicted at a lower level?

A. I do not think cannabis creates a progression. I think if someone is a regular user and they encounter social problems which they may want to escape from, they are more likely to develop into a heavy user than someone who is not a regular cannabis user. I do not think there is a natural progression. I think that is dependent on the individual and the individual's circumstances.

567. With people who would use cannabis for therapeutic purposes, once the need for the therapeutic use has gone would they still carry on using cannabis or would they tend to stop once they have solved their medical problem, other than psychiatric problems, shall we say?

A. The majority of them say that they would not continue using cannabis. There are some medicinal users who have been recreational users as well and therefore it is slightly more difficult to try and suggest what is going on there. I tend to believe that they would give up cannabis if for some reason they did not need it for therapeutic use. I can say that because in observing people suffering from multiple sclerosis for instance, only a very small amount of cannabis is needed to reduce involuntary spasms or to alleviate certain amounts of distress, so they will quite regularly smoke maybe only a third of a joint or half a joint which will sit in their ashtray until three four hours later on in the day, and they will use that if they

14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Soulsby of Swaffham Priory *contd.*]

need to. This would not happen with a regular recreational user.

568. So the possible corollary to what you are saying is that in therapeutic use the danger of users becoming addicted is much less than people using it as recreational use?

A. Yes indeed. I think this will depend on dosage. I have spoken to some therapeutic users who have enjoyed taking too much. You might find that there will be some who would experiment in taking more than a recommended dose but I think in the main there would not be any progression on to addiction because of therapeutic use.

569. The final point of this question is, do all regular and heavy users become tolerant to the psychoactive effects of the drug?

A. Yes, they do.

570. So that means they need to take more and more to get the same effect?

A. Yes. Indeed for the heavy user they are throwing money down the drain. If they stopped using for just a couple of weeks their tolerance would drop back down again to a point where they would receive the same effects with about an eighth of an ounce instead of an ounce. There seems to be an eight-fold difference between regular and heavy use. It is quite a considerable gap.

*Lord Rea*

571. I think it has been said that it is difficult to separate the psychoactive effects from the therapeutic effects, but from what you have just said it would seem as though the therapeutic effects, for example for muscle spasms in people with MS, can be achieved by doses which are below those that would satisfy a regular user.

A. Yes indeed.

572. Would you say that very small doses that can work therapeutically do or do not have psychoactive components?

A. If they do they seem to be so small that they are not noticeable by the person applying the therapy, so they will feel the relief by, for instance, a spasm disappearing, but not feel any sense of disorientation or being stoned. This also seems to apply to people with chronic pain who, for some reason, seem to be able to consume quite a substantial amount of cannabis and not be particularly stoned. I do not know why that is. I cannot offer an explanation on that one.

*Chairman*

573. Can I go back to the question Lord Dixon-Smith asked you as to what adverse effects heavy users get. You mentioned the "whitey", but what else?

A. I think a "whitey" is something that a heavy user would experience very little indeed because by that time their tolerance would have built up. What they tend to suffer from perhaps more than anything is an inability to get anything done. In the same way that, as I suggested earlier, someone who was poor

would feel that poverty was less of a problem if they were consuming cannabis, almost anything for the heavier user becomes less of a problem, and therefore they find it difficult to get on. That will stop however when they have finished using cannabis. I have not seen any indication in people who have been heavier users continuing to be what might be called slovenly.

574. You have not seen much sign in the people you have been studying of the reported adverse effects of cannabis?

A. No, I have not. Some of them of course might be very difficult to detect. If there are some effects on memory, whether it be short term or long term, from heavy users, it might be very difficult to detect. It is easy to detect when someone is stoned. Their short term memory is affected.

*Lord Dixon-Smith*

575. Arising out of this observation of users, do you have amongst those you are observing, people who have been using cannabis 40 or 50 years? If one looks at heavy tobacco smokers who have been smoking all their lives, by that stage you are beginning to expect to see carcinogenic effects quite soon, and I wondered if you had got people that you were observing with that sort of side effect coming along, or are they all in fact a half a generation younger so they have not got there yet?

A. No indeed. I know a number of cannabis users who are between the ages of 50 and 80, and they have used cannabis heavily throughout their lives apart from one period, and this is something that I find very interesting indeed. Someone who is a heavier regular cannabis user tends to stop their cannabis use around the age of 30 or 35 and then recover it at around the age of 55. In discussing this with my head of department, the only thing that we could tie it down to was some kind of kinship cycle and whether this was connected to the creation of a family and responsibilities in mid life, and a decision being made to reduce their cannabis use, but those people tend to pick it back up again in their mid to late fifties. On the particular question you asked, I find that very difficult to say from my perspective because often these people have been heavy tobacco smokers as well.

576. That break in use is quite a clear distinction between cannabis users and tobacco users who tend to go on without a stop.

A. Yes.

*Lord Kirkwood*

577. You were talking about "whities" and the unpleasant effects. Are there any further unpleasant effects associated with the overdose apart from things like loss of memory, and would you say that these could be associated with either impure sources of cannabis or the type of cannabis, or is it any cannabis that gives these unpleasant effects?

A. The unpleasant effect comes infrequently throughout a cannabis user's life and it tends to be concentrated most at the beginning. It is connected often with alcohol consumption. It is called a



14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Kirkwood *contd.*]

"whitey" because they appear to go white. The blood drains from their face and they do not look particularly well. They have an incredible sense of their own mortality, perhaps much more so than being excessively drunk on alcohol. Cannabis at that stage almost makes one paranoid about one's death in an excessive way. This seems to allow people to regulate their cannabis use in order to avoid a "whitey" because it is such a distressing thing to happen. I do not know whether there are further medical effects that can come from impurities and this is a research project I am hoping the Scottish Office will move on, where I will go round the country collecting cannabis resin and take it to the police forensic lab in Edinburgh where we will try and find out what is actually in the cannabis resin. We know that diesel and petrol will be absorbed because of the way cannabis is often imported into this country. We know that there are substantial additions of pieces of plastic, metal filings, all sorts of physically heavy objects being put into cannabis resin to increase the weight, but there are also things like ghee, wax, henna, various additives, boot polish even, which I suspect must be horrendous things to consume.

578. So it could well be the effect of just poor adulterated cannabis rather than cannabis itself, the "whitey"?

A. It could be.

*Lord Porter of Luddenham*

579. I want to ask you about problems of impurity of the cannabis resin. First of all, you say in paragraph 2.1 of your excellent brief to us: "The most common form of cannabis used in the United Kingdom is imported cannabis resin."

A. Yes.

580. I was rather surprised about that because I thought the cannabis weed was commonly used. If you buy imported cannabis resin how do you smoke it? How do you take it?

A. The most common form comes from North Africa. It is generally known as "soap bar" or "dark rocky". It is called "soap bar" because of the shape of the thing that it appears in, and it is called "dark rocky" because it is dark and it comes from Morocco. Generally it will be resin extracted from the flowering tops of the female, rubbed and pressed into a block. If one is smoking a joint, either a king sized cigarette paper will be used or several small cigarette papers will be glued together. A cigarette will be unzipped and the tobacco tipped into the newly formed cigarette paper wrapping.

581. The tobacco?

A. Yes. In the construction of a joint almost always tobacco is used. Then cannabis resin will be heated and crumbled into the tobacco, so the dosage for a recreational user is simply by eye. They just judge how much they are used to and they will put that in.

582. So we have no control—you just cannot smoke cannabis without smoking tobacco? Is that so? What would be the alternative?

A. No. Some people will smoke cannabis in pipes. A joint is the most common form of it being smoked.

Some people thoroughly enjoy the procedure of bringing out the little box and rolling the joint and having it nicely prepared at the end. Some people roll joints because it is easier to smoke in public if they prepare small joints. Some will even scoop the tobacco out of a cigarette, mix it with cannabis and then pop it back in so that what they are smoking looks just like a cigarette. However, small pipes can be filled with cannabis resin.

583. Just the resin?

A. Yes.

584. Pure resin?

A. Yes. And it is like a pipe going out all the time. You have to constantly heat it to get the smoke. There are a number of different pipes available. There are a number of different water pipes available where the smoke is drawn through water to cool it. And there has been an upsurge, I would say in the last five years, of what is called a "bucket bong" where a two-litre plastic lemonade bottle is sliced off at the bottom and a funnel is put at the top where the cannabis will be set alight. This is put into a bucket of water so that the water fills the two-litre bottle and then the cannabis is lit, the bottle is lifted up so that it fills with smoke and then they either take off the funnel and just suck very hard or they suck and push the bottle back into the water so that the smoke is forced into their lungs.

585. Can you comment on the problems of impurity and quality control?

A. There is almost no quality control. The quality control is minimal in that someone who was dealing cannabis could only get away for so long with selling something which was substandard. However, the quality level which is acceptable is this usually bastardised Moroccan resin, so you are starting off at a fairly low quality product, certainly much lower than one would purchase in Holland in the coffee shops.

586. And this comes from all over the place, various countries, and different kinds of hash and so on.

A. Yes. There is nothing like the range of cannabis available that there was in this country maybe 20 years ago. There used to be a considerable amount of variety. It would come from Thailand and Nepal and India. At the moment it is coming principally from Pakistan and North Africa, usually through Spain or Holland and arriving here.

587. So the problem is not getting worse in that sense. It is getting easier, is it? There are fewer kinds of cannabis?

A. There are fewer kinds but there are problems associated with it. Because there are fewer kinds there is less incentive for someone to visit the dealer regularly, whereas before they could go once a week and get a different variety, a different brand if you like, and it would give them a different experience. Now the likelihood is that they will get the standard cannabis resin or worse, so they tend to buy more than they would have bought 10 or 15 years ago. Of course, if a police constable enters your house and you have an eighth of cannabis, currently not very much would be done about it. It would be confiscated and you might be reported to the CPS or the

14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Porter of Luddenham *contd.*]

Procurator Fiscal. You may be fined, but if you have decided to buy an ounce because you cannot be bothered going back to the dealer for another month or a month and a half, then you can be in serious trouble.

588. You say quality control is not completely non-existent because the market tends to regulate itself.

A. Yes.

589. Which means that the user can detect a bad product to some extent?

A. Users who are experienced will be able to detect a bad product. It is often a combination of smell and texture. If there is a great deal of henna in the product you will be able to smell a sweet aroma from the henna. If there is treacle in it then you can detect the smell of treacle. If there are petrochemical products either absorbed or added, then you tend to get a smell of diesel. When cannabis resin is heated it is fairly soft and malleable. Sometimes when it has been bastardised by adding soil and ghee and what-not, it makes the cannabis crumble into very hard and brittle lumps, so if you are experienced then you can tell that it has been contaminated. However, you often do not know that until you get home and that purchase will have already been made. The dealer has been able to con so many people on that bulk purchase that he has made. The next time you go back to that same dealer you will make sure that it is tested before you leave.

590. In a country like Holland where it is not illegal, for whatever the reason, is there any more quality control than there in this country?

A. Yes, there is.

591. Well, there is none in this country.

A. Having the choice made available to you and considerably more education in Holland about cannabis use has meant that people are much more interested in pure cannabis than just whatever they can get. It seems to have encouraged people to smoke cannabis herb rather than resin, so in Holland many more people smoke herbal cannabis than resin. It tends to be that the resin sold in coffee shops is sold to visitors coming from other countries.

*Chairman*

592. There will be less contamination?

A. Yes. There is almost no contamination of herbal cannabis even in this country.

593. The control of quality is almost impossible anyway, but the control of dose is. Those who smoke cannabis, do they calibrate their own dose?

A. Yes, and this is often just done by eye and experience. There are some therapeutic users who subdivide their own cannabis into little amounts because they have become used to what is right for them. Sometimes, particularly with MS sufferers, they are not particularly thinking clearly about how much cannabis should be put in, and they may for instance be halfway through rolling a joint and completely forget that they have added the cannabis and therefore will put more in and that can become uncomfortable for them. In terms of recreational use,

it is simply down to eye and someone who is experienced will be able to tell after the first consumption of a particular amount whether they ought to be adding more or less.

*Lord Rea*

594. You have already said that people used to try cannabis from different sources to get the different experience. Is this actually due to the cannabis itself having different qualities depending on where it comes from, or is it simply because the strength is different, and is it in fact a really different experience or is it just perhaps subjective?

A. Although I cannot tell you why, I am sure it is the cannabis itself that is different and different strains are producing different effects. It may be that it is the relationship between the different cannabinoids and their percentages in relation to one another that make a difference. I have no idea why it would be but I am absolutely sure that the cannabis itself creates a different effect. There were notable and extreme ones mentioned in my report. Thai grass tends to give someone a very light and kind of airy "stone" as it is described, and the effect is principally cerebral. It is mainly in their own mind. Heavier cannabis like Nepalese black or strong African grass has a very distinct physical "stone" and the whole body becomes relaxed and, if too much is consumed, completely immobile; and there are ranges in between.

*Lord Porter of Luddenham*

595. We have been told a number of times that there are many other compounds besides tetrahydrocannabinol in marijuana or whatever, and the synergistic effects between these are important, and would be of therapeutic use and not just—

A. This is something that I have spoken to with Dr Roger Pertwee whom you have also heard from, and I communicate with Dr Pertwee quite often. I have suggested to Dr Pertwee that it is important to look at the different types of cannabis as well as the constituent parts of cannabis. At the moment it would be incredibly difficult to conduct these kinds of trials but I think perhaps at some point in the future if it were possible then that would be a worthwhile thing to do because they are so distinct in their effect.

596. But of course with 60 different cannabinoids it is almost impossible.

A. It could be a nightmare. However, I could almost say myself that if someone were applying therapeutics for multiple sclerosis they would be far better smoking a little bit of Thai grass than some heavy Nepalese resin, but if someone is using it for chronic pain they would be much better served using Nepalese resin than Thai grass.

*Lord Rea*

597. Do all these different strains come from the same plant that is called cannabis Thai grass?

A. Yes.



14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Lord Rea *contd.*]

598. Or are there actually subspecies which, if we looked harder, we would be able to identify at the plant stage?

A. I think that is a botanical argument that was unresolved. I think that the opinion is now that it is a single species and that there are a number of variants, but I could not talk properly on that.

*Lord Dixon-Smith*

599. The differences could presumably be in cultivation technique which would tend to produce a slightly different balance in the plant?

A. Cultivation technique is very important and in a sense a poorly cultivated Thai grass would not be as good as a well cultivated Thai grass, but it is still going to be distinctly different from a poorly or well cultivated Durban Poison or some other kind of strain. Indeed, there are ranges within what you might expect from a single type of plant, depending how well it is cultivated.

600. What we actually have then is a species of plant with a wide global distribution?

A. Yes.

601. And the variations within the plant are probably due to the local topography?

A. Yes, and it ranges from hemp, which would be simply a fibrous plant with almost no psychoactive effect, up to something that is very powerful and growing wild in central Africa. However, the whole thing is complicated even further by people making hybrids from strains that they have cultivated specifically for their effect.

*Lord Porter of Luddenham*

602. So it is not just the horticultural differences from one place to another. Although they may be the same species there will be many different varieties?

A. Yes, and these have been engineered principally in Holland but also in the States.

*Lord Dixon-Smith*

603. But we are dealing in effect with exactly the same differences that you get in vines, the differences between French vineyards?

A. Yes.

*Lord Butterworth*

604. In your conclusions you say, do you not, that you think there is a need for more research into the potential for effective therapeutics?

A. Yes.

605. What would you like to say to us about how you think research in this area might be conducted?

A. I think it is terribly important to investigate how we can capture the importance of the immediacy of effect from smoking without introducing the hazards of smoking itself. Therefore, an investigation into various forms of cannabis being ingested quickly for people that require it for involuntary spasms or whatever. The other thing

would be to try and investigate to what extent the varieties of cannabis will affect the therapeutic user.

606. You mean it is almost a problem for Kew Gardens?

A. Yes, almost, I would say, in many respects. It could be terribly easy to produce Dronabinol and distribute this as cannabis in pill form and make it suitable for chronic users and as an anti-emetic, and completely miss a whole range of variations coming from different plants only to discover 50 years down the line that if we had used a different plant then maybe one milligram would have been all that was needed instead of 20. Those kinds of things might make a difference.

607. You go on to say that the research should be extended to illuminate consequences for the recreational user. We wondered what you really meant by that. Will you elaborate?

A. As an example that has come out today, if it were discovered that the cause of a "whitey" and the distressing effects were indeed due to contaminants and not cannabis itself, this would be terribly important for our perspective on recreational users. If we discovered that there are very definite problems with memory associated with Nepalese cannabis and not so much with Thai cannabis then that might be important for the recreational user, so it is more a sense of being concerned that there are anyway 7.5 million people using this in the country, and that somehow they ought to be educated about what they are doing.

*Chairman*

608. Have you any experience of patients using Nabilone or Dronabinol?

A. Yes indeed. In fact, my mother was given it when she was at the Western General in Glasgow and getting chemotherapy treatment for lung cancer, and she was put on trials for this and she found it efficacious. She found that it worked for her in that on the occasion that it was not introduced into her—I think it was introduced into a drip—she vomited considerably. The other people who I have known using Nabilone are through stories that I have been told in communications with people who have suggested that it worked but not perhaps as well as natural cannabis. I question that of course because they may well be people who are also interested in recreational use, so to give a clear answer on that I would need to try and find out what the motives were behind that kind of response because I certainly know that some people are using Dronabinol or Nabilone who do get an effect. It does work for them.

*Chairman*

609. Are you aware of the work of M J Atha at the Independent Drug Monitoring Unit who also has conducted large scale surveys of regular cannabis users?

A. Yes.

610. How closely do his results marry with yours?

A. There is much that he says which I can agree with. Obviously, when considering someone else's

14 July 1998]

MR NEIL MONTGOMERY

[Continued]

Chairman *contd.*]

work often the problems are the things that come to the surface, so on the one hand the work is fair, but I suggest it does not give a complete picture of who is using cannabis principally because the main sample came from music festivals. Secondly, although it was mentioned in part of his report, there was no clear distinction between the consumption of resin and the consumption of herbal cannabis, and because one is twice the rate of the other I think it would be quite important to try and build that into the statistical figures that he is producing.

611. Is there anything that you would think that we should have asked you that we have not?

A. No. I think in terms of your remit you have probably asked as many questions as I could answer for you. It may be that there could be some encouragement to look more deeply into the recreational use of cannabis in this country and see just quite how the legislation that we have actually affects it. My own belief is that the people who are not using cannabis are not using it not because of legislation. They are not using it because they do not want to, and there seems to be in a number of countries throughout the world a figure of somewhere around 15 per cent of the population who are interested in using cannabis and the rest are not. I do not know why it is. I have not looked into that properly. It is a feeling that I have got in that in most places this is a level of use which would remain whether there was legislation or not.

*Lord Soulsby of Swaffham Prior*

612. I was interested in the late 19th century study which showed that it was better to be poor with cannabis than poor without cannabis. If we look at the United States where it has been decriminalised in some states, is there any indication there of certain states where the socio-economic level is lower than others, that problems have or have not arisen? Can we learn anything from different socio-economic groups in the United States on this business?

A. I am not entirely convinced that we can learn much from the United States on this at all. There seem to be no particular economic reasons within states for them to have decriminalised. In some states there has been a strong history of agriculture, so there has been a strong relationship with hemp from a very early period. I think it may be fair to say that people who have become accustomed to the plant itself are less likely to be neurotic about it, if I can say that. I would seriously worry if we pursued many of the convictions of the United States as far as cannabis is concerned.

*Lord Rea*

613. Would you just clarify whether the 7.5 million using it, including Scotland, according to paragraph 2.2 of your paper, are those who have ever used it; and does that include the largest portion, the casual users, people who may have used it many years ago, or is it just people who have used it within a certain period?

A. I am happy to use that figure for my four grades of cannabis users if you like, which does not include someone who uses it once and never uses it again.

*Chairman*

614. Your figure is for current users?

A. Yes. It would include someone who might smoke cannabis four or five times a year at parties and be quite happy to do that on a regular basis throughout their life. What it will not include is someone who smokes once or twice throughout their life.

615. It is said by many of our witnesses that the casual users and even some of the regular users tend to stop when they get to the age of about 30 or 35 because they have been using it in their earlier life.

A. Yes.

616. Therefore the number of current users would exclude these people who had been users and had stopped. Are there two figures? Which is yours?

A. No, I do not think there are two figures because I think in the main cannabis users will go through this change. They may not stop altogether. They may change from being a regular user to becoming a casual user throughout that period. There certainly seems to be a distinct drop in their use, so they would be included in my figures.

*Lord Rea*

617. A number of surveys have shown that if you take the younger age group, it is 50 per cent who have used it at some point.

A. Yes.

618. How about your lot? I am not sure which study you are looking at, if you are looking at people under 25 or under 40?

A. I think there is a considerable number of people under the age of 25 smoking cannabis now. I find it almost impossible to put a percentage figure on it other than to say that almost without exception people whom I speak to below the age of 25 say that everyone they know smokes cannabis.

Chairman: Thank you very much indeed.



---

TUESDAY 21 JULY 1998

---

Present:

|                 |                                |
|-----------------|--------------------------------|
| Butterfield, L. | Perry of Walton, L. (Chairman) |
| Butterworth, L. | Porter of Luddenham L.         |
| Dixon-Smith, L. | Rea, L.                        |
| Kirkwood, L.    | Soulsby of Swaffham Prior, L.  |
| Nathan, L.      | Walton of Detchant, L.         |

---

**Memorandum by the Chief Executive, Medical Research Council**

Thank you for your recent invitation to submit evidence to Subcommittee I on the science behind the arguments over the use of cannabis and its derivatives for medical and recreational purposes. We have written previously to outline Council's activities in the field (*letter not printed*). Concerning your specific questions we will limit our comments to those pertinent to the medicinal use of cannabis and its derivatives.

**(i) CANNABIS IN THE TREATMENT OF NEUROLOGICAL DISEASE**

There are numerous anecdotal reports, particularly concerning patients with multiple sclerosis, indicating that smoking cannabis relieves symptoms. Some attempts to address the question systematically have been carried out (eg Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 1997;38: 44-48). These tend to confirm that patients experience subjective improvement in the spasticity, chronic pain, acute paroxysmal phenomena and tremor associated with multiple sclerosis.

There are also case reports of patients whose symptoms have been satisfactorily treated with cannabis or its derivatives (cannabinoids) (eg Hemming M, Yellowleas PM. Effective treatment of Tourette's syndrome with marijuana; and Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet* 1995;345: 579).

Robust evidence of the efficacy of cannabis or cannabinoids in the treatment of symptoms of neurological disease would require randomised clinical trials with objective measurements of function. In the absence of data from randomised trials—and a search of the biomedical literature does not reveal any—the scientific evidence in favour of permitting medical use must be considered slight at the moment.

The Council has had some preliminary discussions with researchers about the feasibility of clinical trials of cannabinoids (not cannabis) for multiple sclerosis patients. There are real difficulties in designing and implementing such trials but we are hopeful that proposals may be forthcoming in due course.

**(ii) TO WHAT EXTENT IS CANNABIS ADDICTIVE?**

This question can only be answered by recognising that dependence (addiction) on cannabis, like that on all other drugs, is not an all-or-none phenomenon but has different grades of intensity or severity. In most users, who are exposed infrequently to preparations of low potency (eg cannabis leaf used not more than once a week), drug dependence is probably at a low level. Nevertheless, this low intensity dependence may be riskier than heavy use of caffeine-containing drinks such as coffee because there is limited evidence that it carries the risk of progression to more frequent use and to use of other drugs. As the frequency of use and potency of a preparation increases, so does the degree of dependence. A small proportion of users (3 to 5 per cent) who use high potency cannabis resin almost daily are much more likely to show a higher degree of dependence that exerts a major influence on their mode of living. These users are much more likely to suffer harm from both the psychological and physiological effects of the substance and from the possible physical consequences of smoke exposure over and above those associated with a regular smoking habit.

It is useful at this point to clarify the evidence from laboratory studies on cannabis dependence. The prime marker for drug dependence is compulsive use of the substance and this is typically displayed in the laboratory by positive reinforcing effects—ie, the tendency to repeat self-administration of a drug. The older published results with cannabis and its active constituents were largely negative in this respect although there was some disagreement. However, improved methods are now beginning to provide evidence that drugs acting at cannabis receptor sites are repeatedly self-administered.

21 July 1998]

[Continued

## (iii) TO WHAT EXTENT DO USERS DEVELOP TOLERANCE TO CANNABIS?

Marked tolerance to cannabis can develop: we are not aware of any serious doubt or controversy about this question. However, tolerance is but one of the neuroadaptations that characterise drug dependence, the others being sensitisation (typically to effects of drugs to which tolerance does not develop) and withdrawal effects. We are not aware of reports of sensitisation to cannabis although it is too early to conclude that it is absent unless the pertinent experiments are reported. With respect to significance in determining addiction, tolerance is of less importance than withdrawal. The introduction of specific antagonists for cannabis receptors has increased the sensitivity of withdrawal testing and this has strengthened the scientific evidence of a cannabis withdrawal reaction. These results corroborate the clinical reports of a mild cannabis withdrawal syndrome, especially with heavy use of the substance.

## (iv) CONCLUSIONS

The question of potential medical uses for cannabis and its derivatives must be considered quite separately from the question of prohibition of recreational use. Many substances prohibited for recreational use have invaluable and vital medical indications.

Cannabis produces drug dependence, and if it is made more accessible, with fewer sanctions against its use, consumption by a wider population will increase. There must then be a risk that this will increase the total number of people who develop the more serious forms of dependence and the medical complications of prolonged heavy use.

It is particularly important that the potential for new medicinal drug development raised by the likely existence of multiple types of cannabis receptor is not stifled by considering all cannabis-like compounds as medically unacceptable because of the abuse potential of the natural product. It may be possible to develop novel compounds in which the medical benefits are enhanced and the abuse potential is diminished. However, such lines of work will not proceed if all cannabis-like compounds are banned. The MRC would be supportive of funding well conceived clinical trials in this field provided the quality standards necessary for such trials can be met. It is important to evaluate, in a rigorous manner, whether cannabis or cannabinoids do indeed offer any relief of symptoms in neurological disease. Without such evidence the debate as to the therapeutic benefits of cannabis and its derivatives will continue in an uninformed manner.

I would welcome the opportunity to discuss comments with the Committee if that would be helpful.

G. K. Radda

8 May 1998

## Examination of Witnesses

PROFESSOR GEORGE RADDA, Chief Executive, and PROFESSOR TREVOR ROBBINS, Chairman of Neurosciences Board, Medical Research Council, were called in and examined.

*Chairman*

619. Gentlemen, thank you very much indeed for coming to talk to us. Perhaps you could start by introducing yourselves?

(*Professor Radda*) I am George Radda, Chief Executive of the Medical Research Council. I have with me Professor Trevor Robbins from Cambridge University who is chairman of our neurosciences board.

620. Would you like to say anything to add to your written evidence before we begin the questions?

(*Professor Radda*) We do not specifically wish to add anything. We are happy to answer the questions that you want to throw at us.

621. In February 1998, you had three research projects in the field, one led by Dr Pertwee and two by Dr Kendall of Nottingham. Has the position changed?

(*Professor Radda*) No. We still have those research projects. The one by Dr Pertwee has now finished and it resulted in a publication of a paper in the British Journal of Pharmacology. The paper described the effects of cannabinoid receptor ligands on electrophysiological properties of myonetric

neurons. It provided some useful basic information on these receptors' behaviour. Dr Kendall's small project is now also finished. That was on neurovascular receptors for cannabinoids. It is essentially a negative result. He has developed new methods for looking at receptors. His second project is still ongoing and we do not yet have a report on that.

622. We have received evidence from both these gentlemen and I imagine you do not have any further comments?

(*Professor Radda*) No. We have read the evidence and I do not think we have any comments.

*Lord Soulsby of Swaffham Prior*

623. In your submission you state that cannabis produces drug dependence. We wonder how strong the evidence is for this and approximately what proportion of cannabis users this involves.

(*Professor Radda*) Perhaps I could just start off and then I will hand over to Professor Robbins who is much more expert in this field than I am. It is true that repeated administration to both animals and man provides tolerance and dependence. I think it is



21 July 1998]

PROFESSOR GEORGE RADDA AND PROFESSOR TREVOR ROBBINS

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

important, in the setting of this inquiry, to differentiate clearly between addiction and dependence. With that background, I will ask Professor Robbins to expand.

(*Professor Robbins*) Of course, it is very important to define exactly what one means by dependence, but we can take as a working definition the criterion that people need the drug as part of their every day life in order to function at their own level. Obviously, there are many ways one can measure dependence, but perhaps one hard nosed way is to look at the number of individuals who are in therapeutic regimes specifically for the cannabis dependent syndrome. The data that are available are from America, from the National Institute of Drug Abuse, and on the Worldwide Web they have given out information that there are 100,000 such individuals currently undergoing this type of programme. One has to measure that against the number of individuals who are taking cannabis regularly and of course we have to define what we mean by that. If one means by that more than once a week, then approximately there would be five million individuals in the US, which gives us a rate of two per cent therefore showing dependence. That would be a conservative estimate because there must be many individuals who have not yet signed up for such programmes. I would say that, at least in the American scene, two per cent would be a minimal estimate. If one takes a laxer criterion of cannabis use—for example, once a month—then one is talking about ten million individuals and the rates would correspondingly reduce.

624. You would maintain that this does produce drug dependence, regardless of use, whether it be therapeutic or recreational? From other witnesses we have had evidence that therapeutic use tends not to lead to dependence once the therapeutic necessity has disappeared.

(*Professor Robbins*) I am not sure that information exists on that particular division but I would not be surprised if it were the case that dependence figures are largely based on heavy intake in the recreational population.

625. Might it also be that cannabis quality varies enormously so that you do not really know?

(*Professor Robbins*) One always has that caveat and indeed of course all of these data are plagued by problems of dosage and regimen, which obviously affect the degree of pharmacological effect.

626. Apparently minimal use might in fact be much more if you had a very strong product?

(*Professor Robbins*) Exactly.

Chairman

627. When you said that your definition was those who were undergoing therapeutic regimes for dependence, what sort of regime are you talking about?

(*Professor Robbins*) The treatment regime, I imagine—I am no expert in this area myself—would involve the normal cognitive behavioural package that is being piloted in America widely for different forms of drug abuse.

Lord Rea

628. How do recent scientific discoveries of multiple receptors for cannabinoids and the existence of endogenous cannabinoid compounds such as anandamide, affect the likely development of research?

(*Professor Radda*) Obviously, any fundamental understanding of the mechanism of action of these substances is going to be very important. The discovery of these receptors I think changed that substantially. There are now two receptors known. If one compares this with other drugs, there might well be many more yet to come. We are beginning to see the mechanism of how they act on the receptors.

(*Professor Robbins*) Cannabinoid pharmacology has exploded in the last decade and this is a very exciting area of basic research. We now know, as Dr Radda has mentioned, there are two cannabinoid receptors, one prevalently in the central nervous system. We know the location of these receptors, that they are in the hippocampus and structures as the cerebral cortex and the basal ganglia which are all involved in higher functions of various forms or another. These cannabinoids have been linked to many distinct types of function, including motor effects and cognitive effects as well as motivational syndromes. The discovery of the cannabinoid receptors of course has implications for the endogenous substance (possibly anandamide) which must normally occupy those receptors. As many of you will know, we have learned many lessons from the opiate receptors, for example, in that regard, with the discovery of the enkephalins and endorphins. This will continue to be a very exciting and active area of research. The discovery of antagonists is also exciting from a strictly pharmacological point of view because it provides a way of specifically attributing particular effects of the tetrahydrocannabinoids to particular receptors, which is a very important pharmacological criterion or milestone. Some of these agents may be of therapeutic interest in their own right. I know of some attempts to test the anandamide antagonist as a possible cognitive enhancer. This is being developed by a company in France. I think this pharmacology opens up all sorts of exciting possibilities, including the well known possibilities in analgesia and treatment of other neurological syndromes.

629. Are you getting enough high quality proposals coming your way to investigate and explore this field?

(*Professor Radda*) I think you see from the amount we support at the moment that we are not. The Medical Research Council system is that we fund the best proposals, irrespective of their field, although we identify priorities and addiction and research in relation to that as one of our priority areas. We encourage applications, but we do not ring fence funds around particular areas. We expect to support the highest quality applications, taking into account our strategic priorities in the final awards.



21 July 1998]

PROFESSOR GEORGE RADDA AND PROFESSOR TREVOR ROBBINS

[Continued]

*Lord Dixon-Smith*

630. Do you think that you do not get proposals coming forward in sufficient numbers because of the regulatory hoops that people who wish to research this field have to jump through in order to get going, or is it a result of, if you like, the relatively easy availability of the substance of cannabis to the population at large, and of course the immense complexity of dealing with a substance that has very variable quality and an immense combination of cannabinoids within it?

(*Professor Radda*) There are a number of different issues raised there. In terms of the regulation, I suspect that if you have a good research programme there is no difficulty in getting the proper permission from the Home Office. Indeed, we have a list of people who are doing research not with MRC support but who have permission for that. Scientists are now very used to dealing with regulations in all kinds of experiments—animal experiments, human ethical issues and so on—so I do not think the regulation is a problem.

*Chairman*

631. Is it that you get lots of applications and they are just of poor quality?

(*Professor Radda*) We have not got many applications. I do not have the number for how many applications we have had in recent years, but by and large we have had very few.

(*Professor Robbins*) There is certainly little barrier to doing effective research in the basic neuropharmacology of addiction. For example, on heroin addiction, which is a very serious problem, I am actually part of a programme grant which is researching amphetamine and heroin addiction. We have had no problems in acquiring supplies of heroin appropriately regulated for that purpose. In that basic type of research, it is quite clear that there are implications for topics such as cannabis dependence, because although the cannabinoids work at particular receptors they do actually have some action on the same systems that are influenced by drugs such as amphetamine, for example, in the brain, notably the ventral striatum.

*Lord Butterfield*

632. Are there many other sources of research funding for this kind of work with cannabis which are in competition with MRC funding?

(*Professor Radda*) I am sure the Wellcome Trust would consider applications in the field and I know they support some. There are some other charities that support, but the major funders would be the Wellcome Trust and the Medical Research Council.

633. Do we know how many projects the Wellcome Trust are supporting?

(*Professor Radda*) I am afraid I do not know the answer to that but I am sure the information is available from the Wellcome Trust annual report.

(*Professor Robbins*) They used to support some of Dr Pertwee's research.

*Lord Walton of Detchant*

634. We have had a lot of evidence to suggest that long, continued, high usage of cannabis does lead to cognitive decline and a degree of intellectual impairment, but we have also had some evidence more recently to suggest that activation of cannabinoid receptors may have in fact reduced the mobilisation of free radicals and may therefore have a protective effect. Would you have any comment upon the possible neuroprotective effect of cannabis and also upon whether there is any evidence to suggest that the cannabinoids may stimulate the production of endogenous endorphins and therefore increase analgesia?

(*Professor Robbins*) I have nothing in particular to say about the free radical aspect. As with any drug, there are always mixed effects, some of which will lead to deleterious actions and some of which will have positive effects. If you look at my own presentation to the Royal Society, I was able to find some evidence that cannabinoids, in certain situations, produced minor enhancement of certain aspects of cognitive function, so one has to be very careful about calling cognitive function a unitary thing. There are many aspects of this and I think that would be my general answer to that type of question. On balance, it is apparent that long term chronic, severe, high dosing of cannabis does lead to quite consistent, although not absolutely catastrophic, cognitive deficit, certainly not on a par with dementia, for example, or amnesia.

635. Turning now to multiple sclerosis, we have had a great deal of evidence, much of it anecdotal, some of it perhaps more scientifically based, to suggest that cannabis smoked or taken in other forms may have a beneficial effect; but most of the evidence suggests that that beneficial effect is upon the relief of pain and flexor spasms and spasticity. We have not had any convincing evidence to indicate that it may have any effect upon the course of disease. I was a little puzzled therefore by your comment to the effect that your discussions with people in Exeter had dealt with the question of an ongoing debate about outcome measures in MS. I should have thought that to measure the outcome of a treatment and its effect upon spasticity would not be so difficult. Of course, outcome measures have been well designed for looking at the course of the disease when treated with beta interferon. Would you care to comment?

(*Professor Radda*) I think that Professor Robbins is working on some outcome measures in relation to MS. That was part of the background to that statement. You are right of course that there are certain outcome measures and most recently a lot of people are beginning to use MRI to look at the progression of the disease, but you will know better than I do that it is not that easy to measure the progression, even in the beta interferon trials. You are asking a very difficult question. Unless you are pretty certain that your outcome measures are going to be valid, it is hardly worth getting into a trial, so that is why we were discussing that particular issue.

(*Professor Robbins*) The outcome measures are best assessed by consultant neurologists. The special problem with MS is its fluctuating course and that inevitably confounds any trial attempts, even looking at quite well defined outcomes.



21 July 1998]

PROFESSOR GEORGE RADDA AND PROFESSOR TREVOR ROBBINS

[Continued]

Lord Walton of Detchant *contd.*]

636. I think that is true but most of the evidence we have had has dealt with the chronic, progressive form in which there is quite severe spasticity and pain. Presumably, another factor must be the difficulty of getting a preparation not smoked which actually produces fairly consistent blood levels to use in such trials. Is this another problem that you have been considering?

(*Professor Radda*) In terms of single substances, of course, the preparation is probably not a major issue. It is a question of whether you want to use a single substance or mixtures of substances and do you want to compare orally administered preparations with what you might get in smoking. Those are issues that there are discussions about.

637. One of the things that we have heard from many of the MS sufferers is that some of them have tried nabilone, for example, and have found it much less effective in their view than cannabis. You know of the work of Dr Guy and GW Pharmaceuticals on the production and preparation of natural cannabis. Is this something that you would be interested in pursuing if an appropriate application came before you?

(*Professor Radda*) Yes indeed. I think that comparison would be an important one to make. If there was a well designed clinical trial to answer that question, it would be important to do so.

Lord Porter of Luddenham

638. Professor Radda, in your evidence to the Committee you said, "Robust evidence of the efficacy of cannabis or cannabinoids in the treatment of symptoms of neurological disease would require randomised clinical trials with objective measurements of function." Then you go on to say that there are no such trials and have been no such trials and nothing is recorded in the biomedical literature. Is your Council considering currently involvement in clinical trials of cannabis or cannabinoids? If not, who is going to do it?

(*Professor Radda*) First, let me say that we are in discussions with the Royal Pharmaceutical Society. A panel is looking into that issue, about the possibility of carrying out some preliminary trials. We are also in discussion with Professor Ernst at Exeter University in relation to some possible trials, so yes, we are discussing the possibility of setting up trials. Perhaps I should say that we are very happy and would be happy to consider applications for trials in this area even out of turn in our usual procedure. Our usual procedure is an annual competition for clinical trials. We receive outline applications once a year which are then vetted by a panel of triallists and other experts and short listed for full applications to be put into the MRC. All clinical trials are in a sense in competition with one another so that the clinicians get a fair crack at getting the best trials supported, but we have said in this particular instance that, if there was a need for clinical trials in this area, we would be prepared to consider them out of the usual round of consideration of trials.

639. What progress has been made by the working group which is chaired by Sir William Asscher?

(*Professor Radda*) We have a member on that, Dr Imogen Evans. She has reported back to us. They met last on 18 June. The group is trying to produce guidelines for pilot clinical trials. I understand that they have agreed to draw up protocols for proof of principle studies. The end points they have chosen for those trials are pain and spasticity, which are relatively easy end points to measure. They are debating which products to look at and again the design protocol will involve oral administration of both placebo and tetrahydrocannabinol and other standardised extracts. The comparison with pure compounds and a mixture would be made in the trials. They are making progress in designing good protocols and presumably when these are ready they will come to us with a proposal.

Chairman

640. The natural one is an extract of the plant?

(*Professor Radda*) Standardised extracts, one batch per trial, so that it is always the same batch for a given trial, which they have emphasised as being important.

641. And standardised in terms of the THC content?

(*Professor Radda*) Yes, to give the same dose of THC.

Lord Porter of Luddenham

642. You said at the end of your paragraph, "... the scientific evidence in favour of permitting medical use must be considered slight at the moment." That is following your statement that there is no evidence on the clinical trials. Do you feel that, in the light of the evidence which you are now seeking, it may be possible to permit medical use?

(*Professor Radda*) If there is good scientific evidence, it will be possible. You do need to get good scientific evidence, to answer that question.

643. That is what your Council is seeking?

(*Professor Radda*) Yes.

644. Which may lead to permission for medical use later?

(*Professor Radda*) Yes. I had discussions recently with NIH. NIH are concentrating on trials in relation to smoking cannabis for medical uses.

Lord Butterfield

645. We would like to know whether you believe that clinical trials should be confined to synthetic cannabinoids or is there a place for herbal cannabis products in clinical trials?

(*Professor Radda*) We believe there is a place for well defined herbal extracts in clinical trials, but we must know the composition pretty well, otherwise it will be meaningless to carry out those trials.

646. The question carries a compliment to the Medical Research Council's earlier work on digitalis and the development of synthetic digoxin. Would the MRC ever contemplate a trial of smoked cannabis,

21 July 1998]

PROFESSOR GEORGE RADDA AND PROFESSOR TREVOR ROBBINS

[Continued]

Lord Butterfield *contd.*]

which would be comparable to the digoxin leaf which I used to see at Mill Hill 50 years ago?

(*Professor Radda*) We would contemplate a trial, but I think there are certain very important considerations before you would accept such a trial. One is of course that we know that smoking almost anything, cigarettes of any type, has very dangerous effects in relation to producing cancer and other side effects. That is one issue and the other issue is dose and what you deliver. That may be very difficult to control, although there are ways of doing it.

647. Long ago, a young chemist I knew developed an artificial cigarette which involved putting pure nicotine in artificial cigarettes so that people could inhale the nicotine but they would not inhale the tars. I think Dupont made some kind of cotton wool. Is that a development which might be reawakened to the study of cannabis?

(*Professor Radda*) I heard anecdotally about the development that you refer to. I do not think there is any equivalent at the moment, but in principle if somebody could develop that way of delivering inhaled cannabinoids that would be a much more effective basis for a properly designed, well controlled clinical trial.

Chairman

648. You said you would get a standardised product, but it was standardised in terms of THC content. There are 65 other cannabinoids. You will not know which of them are there or in what quantities.

(*Professor Radda*) I do not know the analytical methods at the moment that are available but it is not beyond the wit of modern analysis to actually decide the composition of each of the products properly. After all, with the genome, we are talking about analysing 100,000 proteins at the same time. I suspect that the chemists ought to be able to analyse 60 products. It is not a big thing.

Lord Dixon-Smith: It is not just 60 products, is it, because it is the combination and the proportion. It is a bit like trying to sort out the winning ticket for the Lottery!

Lord Porter of Luddenham

649. I am moved by Professor Radda's faith in chemists. You did say yes, you would consider using herbal cannabis, but we must know the composition. There are 60 cannabinoids but there are 300 other compounds, quite apart from the smoke components. You might, with a major effort and a lot of people, analyse one but is that going to tell you reliably what you get from cannabis in another field?

(*Professor Radda*) No. I am sure it is not necessarily going to give you that answer. One way of doing it and what the Royal Pharmaceutical Society is talking about is using a single batch in the clinical trials so that at least you are using the same product for the clinical trials. That would be one approach without knowing what the full composition is. Of course, in the long run, I have to say that the kind of developments that Professor Robbins referred to in beginning to understand the mode of action of these

substances, by seeing their receptors and the mechanisms, is probably a more effective way of deciding in any clinical sense whether this could be used properly.

650. Do you feel that a herbal cannabis could ever be permitted in general use? For tests of course you can analyse that specific one, but in a broad market is it possible to specify a thing like herbal cannabis sufficiently to make it ever permissible?

(*Professor Radda*) It is the history of herbal medicine that you use herbal medicine and show that there are good medical effects of a particular agent. Then you try and isolate the substance which is largely responsible for that action and then you produce a pure product. This is the history of the pharmaceutical industry in the past.

651. So you are saying that, before it is ever going to be put on the market, it is going to be broken down, analysed and made into pure cannabinoids or something of that kind?

(*Professor Radda*) That would be a sensible way to proceed.

Lord Porter of Luddenham: And you do not see the use of herbal cannabis being permitted.

Lord Walton of Detchant

652. Do you not feel though that, if the MRC were to countenance a trial of smoked cannabis, they would receive a barrage of criticism from many parts of the medical community? More than 20 years ago when I was on the MRC, I remember that, when the annual photograph of members of the Council was taken in the Council chamber, the photographer was about to click the button and somebody said, "We must remove all the ashtrays from the table". They put them on the floor and the photograph came out with the table and the Council, and the ashtrays on the floor! Seriously though, do you not think that smoking would be contrary to modern medical ethics in general terms?

(*Professor Radda*) It certainly would be contrary to what one believes smoking can do to your health these days, yes. I am glad to say that there are no ashtrays at the MRC any more. It is a non-smoking building.

Lord Dixon-Smith

653. The most common way of taking cannabis seems to be to smoke it in some shape or form. The matter is made more complicated because all too often cannabis is added to tobacco so you have a mixed smoking effect. I do not recall hearing that, with people who persistently smoke cannabis through a long period of their lives, there is actually cancer linkage. Is there evidence for this or is it impossible to identify because of the combination effects with tobacco?

(*Professor Radda*) There is some evidence, I understand, that there is an increased risk, yes.

(*Professor Robbins*) I was about to say I did not know of any evidence of additional effects of cannabis on top of the base risk of nicotine cigarettes.

654. It does not make matters worse anyway?



21 July 1998]

PROFESSOR GEORGE RADDA AND PROFESSOR TREVOR ROBBINS

[Continued]

Lord Dixon-Smith *contd.*]

(*Professor Robbins*) No. It does not make matters worse, but of course there is some evidence for other foetal, developmental effects and other deleterious effects of the drug.

(*Professor Radda*) Perhaps to expand on what I said to Lord Walton on that, I am sure that it is against modern thinking that this is the way you should deliver a substance these days, but if there was a real need to do that trial and somebody came up with a hard nosed, well designed trial to show whether it is effective or not, that is something that we would contemplate.

*Lord Rea*

655. One of the possibilities for such a trial we discussed earlier was that the subjects in the trial should be people who have a serious, life-shortening illness. A "compassionate reefer" might be permissible in patients who are suffering very unpleasant symptoms and anyhow have a disease which is likely to shorten their life. There could be a randomised controlled trial on such occasions.

(*Professor Radda*) That could of course be a very good reason for doing a trial. It is not something I am sure we would go out of our way to try and encourage. If there was a really strong case put to us, which was scientifically valid and was the only way to get an answer, we would certainly consider such a trial application.

*Lord Dixon-Smith*

656. Is there evidence which might justify moving cannabis or the cannabinoids other than dronabinol from Schedule I of the Misuse of Drugs Regulations to Schedule II?

(*Professor Radda*) My understanding is that currently the WHO would not agree or at least would not support such a move because, as I think we pointed out, the evidence currently is not there to show that there is sufficient medical use. The British

Pharmaceutical Society is considering pilot studies to try and produce sufficient evidence for such relaxation of the rules to be brought about, moving from Schedule I to II. That is as far as we have got on that.

*Chairman*

657. We have heard a lot of anecdotal evidence about benefits to patients. The volume of anecdotal evidence is fairly large. At what point does such anecdotal evidence become significant?

(*Professor Radda*) Anecdotal evidence, however large in volume, if it is not properly controlled, is not sufficient scientific evidence to take a decision.

658. It is not going to become scientific, but it can become quite voluminous.

(*Professor Radda*) It can be voluminous and therefore there could be pressure to do further work but I do not think that the volume of anecdotal evidence on its own is sufficient to make a decision that this is something that should be permitted for medical use.

*Lord Dixon-Smith*

659. Is this one of those situations where the best could be the enemy of the good? In other words, scientific purity might actually be preventing some people from getting a benefit that would otherwise be available with a more compassionate approach?

(*Professor Radda*) I think this is true of many interventions. In the end, I think one really needs a hard answer.

*Chairman*

660. Do you wish to make any further comments?

(*Professor Radda*) No thank you, my Lord Chairman.

Chairman: We are very grateful for your time and for your answers.

#### Letter from A D MacFarlane, Chief Inspector, Action Against Drugs Unit, Home Office

The Independent report of 22 April of proceedings before the Science and Technology Select Committee's inquiry into Cannabis refers to a complaint made by the British Medical Association that the Home Office "appeared to be dragging its heels in licensing trials for developing drugs derived from Cannabis. There had been no response to 14 requests for licences, the peers were told."

As this is at odds with the information contained in Home Office records I thought I should write to advise the Committee of the factual position. This is that a total of 27 applications have been made, 25 of which have been approved and licences issued; the remaining two have been agreed in principle. Research licences are valid for a three-year period in accordance with administrative policy; that period may be extended as necessary. A list of the currently valid licences is attached.

Lastly I should also assure your Committee that applications for research licences are dealt with as expeditiously as the circumstances allow.

A D MacFarlane  
Chief Inspector

27 April 1998

21 July 1998]

[Continued

**Supplementary Memorandum by A D MacFarlane, Chief Inspector,  
Action Against Drugs Unit, Home Office**

### 1. ACADEMIC PURPOSES

1.1 Attached is an extract of the list sent under cover of my letter of 1 May in which the description of the non-medical research licences has been amplified. As you will see these are licences issued to universities in connection with the teaching of graduate or postgraduate courses, for laboratory study or for reference.

### 2. WORKSHOP

2.1 I should be happy to hold a meeting with researchers to discuss any aspects of the research licensing provisions and procedures but would suggest that this include colleagues from the Department of Health. Whilst the Home Office is responsible for the issue of licences it generally does so in conjunction with the Department of Health particularly in respect of medical research proposals. I am sure your Committee would find such a joint response helpful. It would provide a useful opportunity to highlight some of the complex issues involved such as the supply of standardised cannabis, and the adoption of sound methodologies.

### 3. CONTROL UNDER THE MISUSE OF DRUGS LEGISLATION

3.1 Cannabis was listed in the Schedule to the Misuse of Drugs (Designation) Order 1973 (SI 1973 No. 796) as a drug which has no medical use. The Designation Order was made in accordance with the powers conferred by section 7(4) of the Misuse of Drugs Act 1971 and came into force on 1 July 1973. The designated drugs were also listed under Schedule 4 of the Misuse of Drugs Regulations 1973 (SI 1973 No. 797). Their production, supply and possession was entirely subject to licence granted by the Secretary of State.

3.2 The Misuse of Drugs Regulations 1973 were subsequently replaced by the Misuse of Drugs Regulations 1985 (SI 1985 No. 2066). The 1985 Regulations have five schedules of drugs whereas the 1973 Regulations had only four. The schedules were also re-ordered; the designated drugs (which had previously been listed under Schedule 4 of the 1973 Regulations) were listed under Schedule 1 of the 1985 Regulations as shown below:

| <i>1973 Regulations</i>        | <i>1985 Regulations</i>   |
|--------------------------------|---|
| Schedule 1 (weak preparations) | Schedule 1 (designated drugs)                                   |
| Schedule 2 (morphine etc)      | Schedule 2 (morphine etc)                                       |
| Schedule 3                     | Schedule 3 (barbiturates, weak stimulant and 2 benzodiazepines) |
| Schedule 4 (designated drugs)  | Schedule 4 (benzodiazepines—new)                                |
|                                | Schedule 5 (weak preparations)                                  |

3.3 Cannabis was controlled in the United Kingdom in 1973 as a drug which had no medical use and which could only be used under licence for research purposes consistent with the provisions of Schedules I and IV of the United Nations Convention on Narcotic Drugs 1961. Article 2(5) of the 1961 Convention provides that:

“The drugs in Schedule IV shall also be included in Schedule 1 and subject to all measures of control applicable to drugs in the latter Schedule, and in addition thereto:

- (a) A Party shall adopt any special measures of control which in its opinion are necessary having regard to the particularly dangerous properties of a drug so included; and
- (b) A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party.”

3.4 Our understanding is that cannabis was listed under Schedule IV of the 1961 Convention reflecting the World Health Organisation's view that the drug was widely abused, had no therapeutic value and was obsolete in medical practice. The WHO's view was that there was accordingly no justification for its medical use and advised that prohibition or restriction of such use should be recommended but not mandatory. The background to international control can be found in the Report on Cannabis by the Advisory Committee on Drug Dependence which was published by HMSO in 1968.

3.5 If it was decided that cannabis should be transferred to Schedule 2 the Advisory Council on the Misuse of Drugs would have to be consulted under sections 7 and 31 of the 1971 Act before any regulations under the Act were made. Variation of the designation order and the transfer to Schedule 2 could be affected by amending regulations which in both cases are subject to the negative resolution procedure (secondary



21 July 1998]

[Continued

legislation). Our understanding is that such a move, if decided upon, would not be constrained by international agreement.

3.6 The consequences of transferring a drug from Schedule 1 to Schedule 2 are as follows. Schedule 2 drugs may be prescribed by medical practitioners. Their production, supply and possession is subject to authorisation which is conferred on certain health professionals, pharmacists etc by the 1985 Regulations or on pharmaceutical manufacturers and wholesalers by Home Office authority. Schedule 2 drugs are also subject to certain other requirements including the prescription handwriting requirements (Regulation 15 of the 1985 Regulations) and to the safe custody requirements. Our understanding is that the ability of doctors to prescribe cannabis would be hampered in practice if a cannabis-based medicine had not been granted a marketing authorisation by the Medicines Control Agency (MCA) for use in the United Kingdom.

3.7 If and when the benefits of a cannabis-based medicine have been scientifically demonstrated and a marketing authorisation issued by the MCA, the Government would be willing to come forward with a change in the controls of the misuse of drugs legislation to allow the prescribing of such a medicine. It would be premature to take such a step before then—that is before its safety, efficacy and quality has been established through relevant research, for which licences are available from the Home Office. Research involving clinical trials would also require clearance by the MCA.

#### 4. STATISTICS

4.1 I understand that Malcolm Ramsay has forwarded you the last Home Office statistical bulletin together with some other emerging research findings on cannabis misuse. If we can help with any further information please let me know.

*A D MacFarlane*

Chief Inspector

13 May 1998

#### CURRENTLY VALID LICENCES—ACADEMIC, ETC

|  |  |
|--|--|
| Dr G Hall, De Montfort University                        | Studies in Pharmacology—Recognition and characterisation by sensory, morphological, chemical and microscopical techniques in pharmacy training |
| Dr D Harvey, University of Oxford                        | Studies in Pharmacology—For research, metabolism and spectral studies by mass spectrometry   |
| Professor F Evans, University of London                  | Studies in Pharmacology—Teaching of pharmacognosy to graduates   |
| Professor M Rubenstein, Liverpool John Moores University | Studies in Pharmacology—Teaching and research in sources. Nature and analysis of drugs in graduate pharmacy course                             |
| Professor P Redfern, University of Bath                  | Studies in Pharmacology—Teaching pharmacy students to identify crude drugs and their chemical constituents                                     |
| Dr R Morgan, University of Sunderland                    | Studies in Pharmacology—Teaching pharmacognosy and forensic analysis on graduate courses in the School of Pharmacy and Chemical Studies        |
| Dr K Brain, University of Wales                          | Studies in Pharmacology—Teaching graduate and post-graduate courses in the School of Pharmacy, UCW, Cardiff                                    |
| Dr J Smart, University of Portsmouth                     | Studies in Pharmacology—Used in teaching BSc (Hons) Pharmacy degree course   |
| Dr P Dewick, University of Nottingham                    | Studies in Pharmacology—Hold as an exhibit and for use in chemical and microscopical examination   |
| Dr G Lockwood, University of Manchester                  | Studies in Pharmacology—Demonstrations and analytical exercises in pharmacy degree course  |
| Mr M Aitken, University of Brighton                      | Studies in Pharmacology—Used in BSc (Hons) Pharmacy degree course  |
| Dr P Houghton, Kings College London                      | Studies in Pharmacology—Research and teaching at post graduate level   |
| Professor R Richards, The Robert Gordon University       | Studies in Pharmacology—Held for identification purposes in the teaching of pharmacology and used for occasional short-term graduate research  |

21 July 1998]

[Continued

|  |  |
|--|--|
| Dr C Hunter, University of the West of England | Studies in Forensic Science—Teaching of plant anatomy in relation to forensic microscopy |
| Dr M Cole, University of Strathclyde           | Studies in Forensic Science—Training students in drug profiling and impurity analysis    |
| Professor D Cowan, Kings College London        | Drug Testing—Held as reference standard for drug testing                                 |
| Dr John Cole, University of Liverpool          | Studies in Psychology—Development work on an animal model for schizophrenia              |
| Dr Pavel Kocovsky, University of Leicester     | Studies in Chemistry—Research in catalytic chemistry                                     |

### Memorandum by The Home Office Research and Statistics Directorate

#### RECENT FINDINGS FROM SURVEY OF ARRESTEES IN FIVE ENGLISH LOCATIONS

##### SUMMARY

The Home Office has recently published the results of a survey—the first of its type in this or any other European country—of the general range of offenders arrested by the police. Among other topics, arrestees were asked about their dependence on a variety of drugs. Cannabis was the prohibited drug on which the highest level of dependence was reported (15 per cent stated that they were currently dependent on it). This result was relevant to the fourth question on which the Sub-Committee requested evidence (“To what extent is cannabis addictive?”). It is discussed below, and placed in context. Initially, it is worth bearing in mind that while arrestees’ drug use is greater than that of the general public, they are one of a number of such groups, with whom they overlap: the unemployed are another example.

##### THE SURVEYS OF ARRESTEES

1. Surveys of samples of the general range of suspected offenders arrested by the police have been carried out on a fairly widespread basis in the United States, although not previously on this side of the Atlantic. In the American surveys, the main object is simply to obtain urine samples which can be tested for drugs; the initial interview is often comparatively brief, and is used above all as a means of establishing rapport with arrestees. In this country, the initial interview has been a more central aspect, designed to explore a wide range of topics relating to arrestees, their lifestyles, drug use and offending. And, as in the USA, the interview is followed by the collection of a urine sample. Both the interview and the urine sample collection are voluntary, anonymous and confidential.

2. Fieldwork took place in 1996 and 1997 in five locations: Cambridge, London (Hammersmith), Manchester (Trafford), Nottingham and Sunderland. Altogether, 839 people were interviewed, representing around 85 per cent of those approached. While juveniles (under 17s) were not approached, or the comparatively small numbers of those arrestees severely incapacitated by drugs, alcohol, communication problems and mental incapacity, the sample was reasonably representative of the general range of suspects arrested by the police, for all kinds of offences, including drugs ones. Further details on sampling are provided in the *Research Findings*, as appended. (Even greater detail on this and all other aspects is available from the longer version of the final report on this project, a copy of which should be in the Library of the House of Lords or can be provided.)

##### THE RESEARCH FINDINGS ON CANNABIS

3. During their interviews, the arrestees were asked whether they had taken (ever, last year, last month, last three days various drugs, including the following, other than on a prescribed basis:

Amphetamine  
Cannabis  
Cocaine  
Crack  
Ecstasy  
Heroin  
LSD  
Magic mushrooms  
Methadone  
Temazepam



21 July 1998]

[Continued]

Diazepam  
 Other tranquillisers such as Librium or Mogadon  
 Barbiturates  
 Diconal  
 DF118s  
 Temgesic  
 Amyl nitrate (poppers).

Additionally, similar questions were asked about glue/gas/aerosol (ie solvents), alcohol, and tobacco.

4. Those interviewees stating that they had ever taken any specific substance were also asked: "Have you ever been addicted to, dependent on or needed the drug?" And, additionally, whether they were currently dependent. Results were as follows:

Table 1: PERCENTAGE OF ARRESTEES DEPENDENT ON SPECIFIC DRUGS

|                        | <i>Ever<br/>dependent</i> | <i>Currently<br/>dependent</i> |
|------------------------|---------------------------|--------------------------------|
| Amphetamine            | 18                        | 5                              |
| Cannabis               | 21                        | 15                             |
| Cocaine                | 7                         | 2                              |
| Crack                  | 9                         | 3                              |
| Ecstasy                | 6                         | 1                              |
| Heroin                 | 16                        | 11                             |
| LSD                    | 2                         | <1                             |
| Magic mushrooms        | 1                         | <1                             |
| Methadone              | 9                         | 6                              |
| Temazepam              | 9                         | 3                              |
| Diazepam               | 4                         | 3                              |
| Barbiturates           | 2                         | 1                              |
| Diconal                | 5                         | 2                              |
| DF118s                 | 3                         | 1                              |
| Temgesic               | 3                         | 1                              |
| Amyl nitrite (poppers) | 1                         | <1                             |
| Alcohol                | 26                        | 16                             |
| Tobacco                | 71                        | 68                             |

Leaving aside alcohol and tobacco, the drug on which the highest level of dependence was reported was cannabis: 21 per cent stated that they had had been dependent ever, while 15 per cent stated they were currently dependent.

5. To some extent, this high level of dependence on cannabis varied—as was true for other drugs—from place to place:

Table 2: PERCENTAGES OF ARRESTEES EVER/CURRENTLY DEPENDENT ON CANNABIS IN THE FIVE DIFFERENT LOCATIONS

|            | <i>Ever</i> | <i>Currently</i> |
|------------|-------------|------------------|
| Sunderland | 9           | 8                |
| Nottingham | 18          | 11               |
| London     | 24          | 18               |
| Cambridge  | 34          | 27               |
| Manchester | 39          | 22               |

6. It is also worth bearing in mind that many of the arrestees stated that they were dependent on various different drugs:

21 July 1998]

[Continued

Table 3: PERCENTAGES OF ARRESTEES CURRENTLY DEPENDENT ON DIFFERENT NUMBERS OF DRUGS (EXCLUDING ALCOHOL AND TOBACCO)

|            | <i>None</i> | <i>1-2</i> | <i>3-4</i> | <i>5-6</i> | <i>7+</i> | <i>One or more</i> |
|------------|-------------|------------|------------|------------|-----------|--------------------|
| Sunderland | 84          | 13         | 2          | 1          | 0         | 16                 |
| Nottingham | 73          | 23         | 3          | 1          | 1         | 27                 |
| London     | 63          | 29         | 7          | 1          | 0         | 37                 |
| Cambridge  | 61          | 32         | 4          | 2          | 1         | 39                 |
| Manchester | 49          | 35         | 12         | 4          | 1         | 51                 |

In other words, a range of approximately between one in seven arrestees (in Sunderland) and one in two (in Manchester) stated that they were dependent on various drugs (other than alcohol and tobacco).

7. As with any answers given in interviews, precisely what respondents meant is open to interpretation. But it is interesting that, among this group, the level of declared dependence on cannabis was very similar to that on alcohol.

8. What possible reasons are there for more arrestees being dependent on cannabis than on other prohibited drugs? One relevant factor is that cannabis was more widely used than other prohibited drugs. Deploying the results of the urine tests, the percentages of arrestees showing signs of use of different drugs were as follows:

Table 4: PRESENCE OF DIFFERENT DRUGS IN THE URINE OF ARRESTEES (N = 622)

|                 | <i>Percentage of arrestees</i> |
|-----------------|--------------------------------|
| Cannabis        | 46                             |
| Opiates/heroin  | 18                             |
| Benzodiazepines | 12                             |
| Amphetamine     | 11                             |
| Cocaine/crack   | 10                             |
| Methadone       | 8                              |

Nearly half of the arrestees who were tested proved to have cannabis in their urine. This is indicative of consumption at least as recently as within the previous two or three weeks or thereabouts (depending on amount consumed). The next most commonly revealed drug was the opiates/heroin group, running at less than one in five arrestees. In other words, the two drugs most frequently revealed by the urine testing of arrestees were the same ones—in the same rank order—as those on which the highest level of dependence was reported.

9. Finally, it is worth bearing in mind that—even though few if any medical services are specifically geared to cannabis—the series of *Drug Misuse Statistics* compiled by the Department of Health does point to cannabis as being a fairly commonly reported main and subsidiary drug of dependence. (I enclose a photocopy of a relevant page from a recent bulletin; if you wished to follow up this angle, it would be necessary to consult the Department of Health.)

10. I am a social science researcher in the Home Office (Research and Statistics Directorate), with specific responsibility for drugs and alcohol research and statistics, and was responsible for commissioning and managing the research on arrestees, as carried out by the University of Cambridge. This evidence is submitted on a corporate basis on behalf of the Home Office (having been shown to the Action Against Drugs Unit).

*Dr Malcolm Ramsay*  
Principal Research Officer

8 May 1998



21 July 1998]

[Continued]

## Examination of witnesses

MR GEORGE HOWARTH, a Member of the House of Commons, Parliamentary Under-Secretary of State, Home Office, was examined; MR JONATHAN DUKE-EVANS, Head of the Action Against Drugs Unit and MR ALAN MACFARLANE, Chief Inspector, Drugs Branch, Home Office, were called in and examined.

*Chairman*

661. Thank you very much, gentlemen, for coming to see us. Do you wish to say anything before we start on the questions?

(*Mr Howarth*) I am George Howarth. I would just like to introduce the two officials from the Home Office with me. On my left is Jonathan Duke-Evans who is the head of the Action Against Drugs Unit. On my right is Alan MacFarlane, the chief inspector of the Home Office drugs branch. You were probably aware that they were coming but that is who they are.

662. Can you tell us what is the process for issuing licences for cannabis research under Section 7 of the Misuse of Drugs Act and what is the fee?

(*Mr Howarth*) Licences for cannabis research are issued to candidates who can demonstrate that there is a legitimate reason for such research. For example, they would have a detailed protocol indicating the methodology, timescales and aims of any such research. Of course, that has to be taken together with the usual safeguards, safe custody and record keeping that would be expected in any controlled drug licence holder. Under normal circumstances, the research would be expected to be laboratory based and conducted at a university hospital or an established pharmaceutical company. For research into possible uses of cannabis for medical purposes, the sorts of conditions that are applied are that an application should be submitted for scrutiny by the Department of Health and the Home Office. The Home Office needs to be satisfied that cannabis is in a form that is not readily recoverable or is administered in such a way that it is not available for misuse. For example, that would include use of hospital premises. Any research should be hospital based and cleared by the relevant ethics committee. Any dispensing facilities should be confined to the hospital pharmacy. There should be a review period for the research. Any project must use an appropriate scientific method, for example, randomised controlled trials. Finally, cannabis must be available in a suitable form for administration in controlled doses. As regards fees, although there are not normally fees, commercial licensees, where there is clearly a benefit to people, are charged an annual fee of either £80 or £160 and that depends on whether or not possession or production is involved.

663. How long have you taken to process the six most recent applications for cannabis research licences?

(*Mr Howarth*) If I go through each in turn, it might be helpful. We can give a written form to the answer so that people can remind themselves of it. The details of the last six applications are, first, the applicant was a Dr Guy. He applied on 9.2.98. The date the licence was issued was on 1.6.98. The time taken was four months. The second was Dr Schon of Charing Cross Hospital. He applied on 20.3.98. The date of issue was 17.4.98. It took one month. The third was Dr Kokovsky of the University of Leicester. He applied on 27.1.98. The date of issue

was 24.2.98, again one month. The next was Dr Cole of the University of Liverpool. Dr Cole did not take up the post until 1.1.98 and the inspectorate visited on 15.1.98. Further inquiries were required for full licensing, so there was a delay until 6.2.98. The next was Dr Todd of the James Paget Hospital. The date applied was 23.3.95. The issue date was 25.5.95. There was a delay due to concerns about custody deficiencies which apparently were then put right before the issue date. Finally, Professor Smith of the University of Oxford applied on 6.8.93. The date of issue was 23.8.93, a two week period. Time was taken during the process of consideration to establish the applicants' bona fides, to check the suitability of premises, safe custody and record keeping arrangements, to advise on regulatory compliance and security, to consult with the Department of Health in cases of medical research and of course finally to generate and record official records and actually issue the licence documents.

*Lord Walton of Detchant*

664. You said in your submission that you have never turned down an application for a licence to use cannabis for research, but Dr Fred Schon told us that you refused him a licence to study smoked cannabis. Was that because he was simply proposing to carry out observations upon the effects of cannabis in a single patient, or was it because you did not wish to give a licence for smoking but were prepared to give one for the use of an oral preparation?

(*Mr Howarth*) I will make a brief response to that but I think you may find it helpful if officials add to what I say. My understanding is that Dr Schon's original application for a licence which he submitted in March was to research the medical effects of cannabis on one particular patient with MS who was suffering from an associated eye disorder, pendular nystagmus. The protocol advised that capsules containing cannabis oils together with identical placebos containing olive oil would be used, although mention was made of the fact that the patient had smoked cannabis illicitly and this had abolished his disabling visual symptoms. That was the basis of the original application. Dr Schon subsequently advised that, for the purposes of his research, he would wish the patient to smoke cannabis as well as having it administered in capsule form. A licence was issued on 17 April enabling both types of administration to take place. In May, Dr Schon wrote advising that he had not thoroughly thought through the number of capsules to be administered on any occasion to obtain the optimal effect and that the research, or at least the administration of cannabis, would take place at a new hospital. No mention was made of whether or not the smoking of cannabis would still be taking place. In view of the significant changes since the original application, Dr Schon was advised to return his licence pending further consideration of his case. Subsequent inquiries did reveal that Dr Schon



21 July 1998]

MR GEORGE HOWARTH MP, MR JONATHAN DUKE-EVANS AND  
MR ALAN MACFARLANE

[Continued]

Lord Walton of Detchant *contd.*]

wished the smoking of cannabis to take place if its administration in capsule form did not prove to be effective. His licence was therefore reissued on 14 July on the same terms as the original one, to enable research to continue allowing for the administration by capsule or smoking.

Lord Butterfield

665. The Committee would be very interested to know if the number of applications for cannabis research licences has increased recently.

(Mr Howarth) A total of 26 cannabis research licences have been issued over the last 25 years. Of those, four have been issued this year, which does suggest that there is a slight increase. Two of those four, Dr Schon and Dr Guy, are for medical research while the other two are for academic purposes. The total of currently valid licences for all Schedule 1 substances other than cannabis is 80. Some are for research but others are for a variety of purposes, such as reference standards, teaching, exhibitions at museums, etc.

666. We have just had the Medical Research Council in and they have made the point that they are not getting many reasonably good applications for clinical trials for them to consider, and we are obviously wondering whether the number of applications for research on cannabis is comparable to the number of research applications for other Schedule 1 substances?

(Mr Howarth) I think perhaps I did cover that area, but could I ask Mr MacFarlane to comment on that.

(Mr MacFarlane) Most of the licences for Schedule 1 substances are asked for a whole variety of Schedule 1 substances because the majority of applications come from academic institutions and they do not know what they may want to be looking at from one time to another. The preponderant number of licences are asked for cannabinoids rather than herbal cannabis when it comes to looking at cannabis and cannabis derivatives. The small increase in applications in recent times for cannabis for medical research does seem to suggest a burgeoning interest which I trace back to a conference organised by the Royal Pharmaceutical Society some 18 months ago to discuss medical use of cannabis.

667. Is there a reserve of investigators of drug addiction and drug problems working on other problems than cannabis who have not yet been directed towards working on cannabis for one reason or another? I just have no idea whether the number of licences for, say, cocaine or heroin research outnumber the number for cannabis or cannabinoid research?

(Mr MacFarlane) The only applications for licences that we deal with in the Home Office are for Schedule 1 drugs. Cocaine is not a Schedule 1 drug but coca leaf is a Schedule 1 drug. If you were wanting to research on cocaine the Home Office would not necessarily know you were doing it. If you were wanting to research on coca leaf we would require to issue a licence. So I cannot give you an answer to that.

Lord Nathan

668. It has been drawn to our attention that of the 15 people charged with cultivation, possession and/or supply of cannabis in therapeutic situations over the last year or so, in 11 cases, as reported, either the prosecution was abandoned, the defendant was acquitted or the sentence was no greater than a conditional discharge, in one case the sentence was 50 hours' community service and of the remaining three we do not know the outcome. Do you consider that this is a satisfactory situation? It seems to conform quite closely to the position in Holland, in accordance with the evidence given to us, that, although cannabis is illegal, enforcement is not very severe upon at any rate the small offenses (if I may put it that way) as opposed to the large commercial undertakings. How do you view this situation?

(Mr Howarth) I think the Crown Prosecution Service has to decide on a case-by-case basis whether or not a prosecution should be brought, and following conviction it is then for the courts to sentence. They have the ability to take into account the particular circumstances of the offence and, indeed, the offender. The production, supply and possession of cannabis are all criminal offenses. If the suggestion of the accused is that the cannabis involved was for therapeutic purposes, that will be taken into account along with many other relevant circumstances in deciding whether to prosecute, and if a prosecution succeeds, on what sentence the courts will decide to pass. If, as a result of all the circumstances, a prosecution is not proceeded with or a light sentence is passed, that is a reflection of the discretion which the Crown Prosecution Service and the courts themselves are able to exercise.

669. And you are happy with that situation or you accept that situation?

(Mr Howarth) I have described what the situation is and I do not think it is sensible, to be perfectly honest, for ministers from the Home Office to be involved in criticism in individual cases of the way the Crown Prosecution Service or the courts conduct themselves. You could look at the way a sample of cases involving other offenses were dealt with and point to apparent trends or inconsistencies, but without knowing the details of all the cases involved and without knowing the proportion of the total number of cases it represents, I think it is very hard to say from the sample you have identified just how significant that is. So my happiness or otherwise is probably not of any great utility in this matter.

Lord Walton of Detchant

670. It is in some respects comparable to the situation we discovered when I chaired the House of Lords Select Committee on Medical Ethics, looking at the issue of mercy killing. There had been 23 cases reported to the Home Office where it had been thought that a relative had helped to end the life of someone in terminal illness, but in no case was there a conviction for murder and in very few was there a conviction for manslaughter because it was felt that no jury would be likely to convict because of the merciful nature of the act. Is that not in some respects



21 July 1998]

MR GEORGE HOWARTH MP, MR JONATHAN DUKE-EVANS AND  
MR ALAN MACFARLANE

[Continued]

Lord Walton of Detchant *contd.*]

comparable to the situation that Lord Nathan has raised?

(*Mr Howarth*) I would not like to be drawn into making those sorts of comparisons. What I would say is that the Crown Prosecution Service, in deciding whether or not to take any case further, will have to set a number of tests against which it will have to judge each case, and I think it would probably be inappropriate for me to speculate too much without knowing the details in any one case as to how those tests were set and how they were passed or otherwise.

*Lord Butterfield*

671. Could I ask whether you have connections with the people in Holland, whether you visit them, whether you know about their present approach to the cannabis problem in their society?

(*Mr Howarth*) Mr Duke-Evans seems to be very keen to get in on this. I have not personally, since coming into office 14 or 15 months ago, had the opportunity to visit Holland to look at what they are doing there. That is not to signify any great reluctance on my part; it is just that I have not found the time to do so, but I have read some of the literature and in the widest context of decriminalisation arguments, I am aware of the somewhat mixed signals that do come out of Holland from time to time, but as regards the specifics, I do not know. Perhaps Mr Duke-Evans would like to add to what I have said.

(*Mr Duke-Evans*) Only in this respect, if I may, that I think the fundamental difference in legal terms is that the Dutch policy is one of systematic non-enforcement of the criminal laws which are still notionally valid in the Netherlands. That is not an approach which is followed in the United Kingdom. Indeed, I think there is a decision of your Lordships' House which states that such an approach would be quite unacceptable in the United Kingdom.<sup>1</sup> So the difference is, as the Minister has said, that in this country each case is dealt with on its merits, both as regards the decision to prosecute and as regards the imposition of any subsequent sentence.

*Lord Kirkwood*

672. The Minister said that he did not want to make a statement about the inconsistency of the courts' rulings. There is not inconsistency, there is consistency; they are very lenient. Does not that imply that the courts do not think very much of the legal situation? Would you not agree with that?

(*Mr Howarth*) I think the courts have to deal with each case on its merits and it is, frankly, not sensible or helpful for me to speculate any further on it.

*Lord Porter of Luddenham*

673. You are talking all the time, are you not, about therapeutic situations?

(*Mr Howarth*) I understand that is the context in which these questions are being asked and I am answering them.

Lord Nathan: The question related to therapeutic situations, that is perfectly correct.

*Lord Porter of Luddenham*

674. Yes, quite, but if I may ask you to add to the information, you have implied, I think, that the very sympathetic treatment of these 15 cases, the leniency of the outcome, is probably because they are therapeutic situations. We have also been considering a comparison with Holland, which I think applies to recreational use as well as therapeutic. So I wonder, could you help us by indicating what happens to the recreational cases, and how many are there compared with the 15?

(*Mr Howarth*) I have not got them to hand. We could probably provide information on that. If I may go back to the original question, I think it is important to understand that it may well be that in some cases people choose to use the arguments of therapeutic use as a defence and so I think the courts themselves have to determine in each case whether or not that defence is a legitimate one in that case rather than a defence that is trumped up for the purposes of the particular prosecution. I would not want to speculate on that. That is why I am loth to get involved in generalising about it. The wider arguments about leisure use and recreational use are, I think, different arguments but since you tempt me into it, I am more than happy to say that my own view is that if we were to go down the wider path of legalisation for recreational purposes, there is only one certain outcome and that is that the use of cannabis, which is what we are talking about, would go up, and the fact that it is illegal obviously acts as a brake on some people who might otherwise use it.

675. I was not wanting to go into that, which is another matter, as you say. I was trying to understand the relevance of the recreational cases to the sympathy which is given to the therapeutic situation. Is the law much less lenient in the recreational cases?

(*Mr Howarth*) I do not think they are as out-of-line as you imply but perhaps Mr Duke-Evans would like to say something.

(*Mr Duke-Evans*) Again I think we are probably all dealing pretty much with anecdotal evidence since there is no foolproof system of having this type of case reported, but I am aware of similar types of cases where suspended sentences of imprisonment have been imposed. So I would endorse the Minister's comment that there is no obvious lack of synchronisation between the kind of outcomes which have been quoted here and the general run of outcomes for recreational cannabis cases. There are many thousands of recreational cannabis cases each year. Imprisonment would be imposed in only a very small minority of such cases and, indeed, cautions and conditional discharges are quite common

<sup>1</sup> *R v Commissioner of Police of the Metropolis ex parte Blackburn*, [1968] 2 QB 118. In fact a judgment of the Court of Appeal, about enforcement of gambling law. "There are many fields in which [the police] have a discretion [e.g. whether to prosecute in particular cases]...but there are some policy decisions with which, I think, the courts in a case can, if necessary, interfere." The court gave as hypothetical examples policy decisions not to prosecute burglary, or theft of goods worth less than £100.



21 July 1998]

MR GEORGE HOWARTH MP, MR JONATHAN DUKE-EVANS AND  
MR ALAN MACFARLANE

[Continued]

Lord Porter of Luddenham *contd.*]

disposals. So it is not clear that you have a very different pattern on the basis of the limited number of cases of which we are all aware.

Lord Nathan

676. Is it the case that you *could*, not *would* but *could*, move cannabis and/or additional cannabinoids, in addition to dronabinol, from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations, with no preconditions other than the advice of the Advisory Council on the Misuse of Drugs and the approval of Parliament? In particular, we have in mind whether you would need as a legal matter either international agreement in view of the Convention or the licensing of a medicine by the MCA?

(Mr Howarth) My understanding of the position is that cannabis and the cannabinoids would have to be treated differently if a move from Schedule 1 to Schedule 2 of the Regulations were contemplated. The difference stems from the fact that cannabis is subject to the 1961 UN Convention on Narcotic Drugs, whereas the cannabinoids are subject to the 1971 UN Convention on Psychotropic substances. So there is a difference there. Our reading of the 1961 Convention is that, if the United Kingdom chose, it could move cannabis from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations without breaching the requirements of the Convention. We would be treating it like heroin, which is classed along with cannabis under the Convention. Rescheduling could be by those means achieved through consulting with the Advisory Council on the Misuse of Drugs and with the approval of Parliament. Our view, though, of the 1971 Convention is that it does not allow the same latitude in respect of cannabinoids as the 1961 Convention allows for cannabis. Then any unilateral move by the United Kingdom to reschedule cannabinoids would, we believe, breach the 1971 Convention. The way to achieve a lesser degree of control would be, through the World Health Organisation itself, to amend the Convention. For neither cannabis nor cannabinoids would licensing by the Medicines Control Agency be a requirement in law to rescheduling. The Government's view is that there are compelling policy reasons for requiring them to be licensed by the Medicines Control Agency.

Lord Rea

677. If you were to move cannabis or additional cannabinoids from Schedule 1 to Schedule 2, would that allow doctors to prescribe them? They would have to be unlicensed medicines and on a named patient basis. And would that allow research to be done without researchers having to apply for a special Home Office licence?

(Mr Howarth) There is nothing in the regulations to prevent any drug in Schedule 2 from being prescribed by a doctor for any organic disease. There are limitations on prescribing cocaine and one or two other products but not those. There is no need for a specific Home Office licence for the conduct of research on Schedule 2 drugs. A general authority is

given by the regulations to institutions the recognised activities of which include scientific research and which are attached to a university hospital.

678. That applies if they were moved to Schedule 2?

(Mr Howarth) Yes.

679. If it were moved to Schedule 2, would the ability of doctors to prescribe cannabis be hampered still in practice if a licensed medicine were not available?

(Mr Howarth) I think this is a reference to our understanding that in prescribing an unlicensed medicine, a doctor does so on his or her own liability. Without the assurance of its quality, safety and efficacy, they might be fearful, in the event of an adverse reaction in a particular case, of laying themselves open to claims of medical impropriety. I think the way the Medicines Control Agency puts it is that a doctor prescribing an unlicensed product or a product outside its licensed indications does so entirely on his or her own responsibility, and they carry the total burden for the patient's welfare and, in the event of an adverse reaction, may be called upon to justify those actions. I think that is the difficulty which you are describing.

Lord Kirkwood

680. If the prescription of cannabis were permitted, but no licensed medicine were available, could the individuals in receipt of a prescription, or someone else on their behalf, apply to the Home Office for a licence to cultivate a sufficient quantity for therapeutic use? If that were not possible, how else might one get over the problem of supply within the law?

(Mr Howarth) The question assumes that it might be sensible to permit cannabis, the safety and quality of which is not certain, for therapeutic purposes, and I think that would be questionable. That said, under the Regulations, doctors and pharmacists acting in their capacities, as such, are given authority to manufacture and supply any drug in Schedule 2. Anyone else would require a Home Office licence to manufacture. While the drug remains in Schedule 1, all activities involving it, including manufacture, supply and possession, can only lawfully be undertaken under a Home Office licence, except in the case of police officers and forensic scientists and the like who obviously have different reasons to do so.

681. I am sorry, but I do not understand whether that included the Home Office licence to cultivate and grow cannabis.

(Mr Howarth) Yes.

682. That would be an acceptable route? Are you saying that?

(Mr Howarth) Yes.

(Mr MacFarlane) If I could add to what the Minister has said, this question supposes that you have already gone through the process of proving a therapeutic use and having it accepted.

683. Of course.



21 July 1998]

MR GEORGE HOWARTH MP, MR JONATHAN DUKE-EVANS AND  
MR ALAN MACFARLANE

[Continued]

Lord Kirkwood *contd.*]

(*Mr MacFarlane*) And then you are talking about where would the source of the material come from and if you are thinking about that in terms of the normal production of medicines through the pharmaceutical industry, if that is the context of your thinking, then the answer is that the growing of the material would be licensed in exactly the same way as you would license the growing of material to produce morphine, that is to say, poppies, so there could be an equivalent regime.

*Lord Walton of Detchant*

684. Under section 8 of the Misuse of Drugs Act, it is an offence to allow cannabis to be smoked on premises. Regulation 13 of the Misuse of Drugs Act allows the Secretary of State to approve premises for smoking for the purposes of research, but not for therapeutic purposes. Let us suppose that we move on to a situation where it becomes legal to prescribe cannabis for therapeutic purposes. If the individuals then smoked it on premises, would the owner of the premises where the smoking took place be liable to prosecution? Could this be remedied by regulation or would it require secondary legislation?

(*Mr Howarth*) The short answers are yes and yes. Section 8 applies, as you rightly say, to occupied premises, and unless the occupier was conducting research on unsmoked cannabis at premises approved by the Secretary of State under Regulation 13, he would indeed be committing an offence under the Act and be liable to prosecution. If the prescription of cannabis were permitted, I understand section 8 could be disapplied by regulation in secondary legislation where a doctor had prescribed it.

*Lord Porter of Luddenham*

685. Minister, do you propose to take up our suggestion of a meeting between yourself and the cannabis and cannabinoid research community to discuss practical issues of research regulation?

(*Mr Howarth*) Yes, I understand that all efforts are being made to organise a meeting with officials from

the Home Office, the Department of Health and the Medicines Control Agency.

686. They have been made?

(*Mr Howarth*) I think arrangements are in hand for that.

(*Mr MacFarlane*) If I could say, yes, we are in touch with the relevant officials in the Department of Health, particularly those who are concerned with people who suffer from Multiple Sclerosis and also with the relevant people in the Medicines Control Agency to arrange such a conference. My main difficulty at the moment is that I am not quite sure whom to invite.

687. Would this be a small private meeting, or a bit of a conference, with a number of people?

(*Mr MacFarlane*) I think that might depend on the degree of interest.

*Lord Rea*

688. Are you aware, Minister, of a body of opinion pressing for the moving of cannabis from Schedule 1 to Schedule 2, and if not cannabis as such then further individual cannabinoids, and how would the Home Office receive such representations?

(*Mr Howarth*) Well, the formal position, and I think it is also reflected in practice, is that we take advice from the Advisory Council on the Misuse of Drugs on this issue and at this time they are not pressing for any such change and their advice is well valued by the Home Office and we would not at this stage want to make any changes since there is no pressure on us from them to do so.

*Chairman*

689. Well, Minister, gentlemen, thank you very much for your time and your answers.

(*Mr Howarth*) Thank you very much.

---

TUESDAY 28 JULY 1998

---

## Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.

Nathan, L.  
Perry of Walton, L. (Chairman)  
Porter of Luddenham, L.  
Soulsby of Swaffham Prior, L.

**Memorandum by Dr Geoffrey Guy**

Dr Guy is a Pharmaceutical Physician with 18 years experience in pharmaceutical developments covering New Chemical Entities, Biotechnology products, plant based medicines and drug delivery systems. Dr Guy has been the physician in charge of over 250 clinical studies, including first dose in man, pharmacokinetics, pharmacodynamics dose ranging, controlled clinical trials, and large scale multi-centered studies and clinical surveys. Specialist areas of interest include Narcotic Analgesics, Hormone Replacement Therapy, Asthma and Eczema.

Dr Guy was the founder of a public drug delivery company and a public phytomedicines company and has established GW Pharmaceuticals Ltd in the UK to operate Home Office Cannabis Medical Research Licences. The licences will enable a planned pharmaceutical development programme to proceed. He has recently agreed a world wide collaboration with the Dutch Medicinal Cannabis breeding specialists HortaPharm BV.

**SUMMARY**

- Herbal Cannabis and synthetic cannabinoid show therapeutic promise
- Existing patient need remains unmet
- Legal framework for research available but too daunting to most pharmaceutical developers
- Very safe material compared to synthetic drugs
- Standardised pharmaceutical grade extracts offer shorter development times
- Purified subsets may offer additional benefits in the medium term
- Individual cannabinoids or combinations of cannabinoids represent long term opportunities
- Cannabinoid ratios and drug delivery hold key to improved therapeutics
- Home Office Licences in place
- Improving regulatory climate
- Viable market opportunity
- Pharmaceutical development programme commencing

Glossary of terms and abbreviations will be found at the end.

**1. RATIONALE AND DEVELOPMENT THESIS**

In considering whether Cannabis and/or its constituents given individually or in combination represent a potential medicine worthy of the enormous effort and expenditure required to undertake a full scale pharmaceutical development programme several factors were important at reaching a decision. Prime amongst these were the following.

1.1. Potential Benefits—Usually when considering synthetic drug candidates suitable for progression into clinical development, one has only pre-clinical pharmacology and toxicology data available. It is often the case that vernacular or ethno-botanical medicines carry with them a history of clinical use. This evidence is often truly anecdotal, and as promising therapeutic effects frequently can not be reproduced by physicians working in the conventional medical setting, such evidence tends to be discounted or ignored. This should not be the case with Cannabis, as the medical literature contains a wealth of corroborative information pertaining to potential therapeutic benefit.

1.2. Low toxicity—We also have a body of literature that chronicles a vast amount of “patient” exposure with no accepted report of lethality this century. The apparent lack of toxicity commends a candidate drug highly for progression into safe human studies.

1.3. Existing Patient Population—The existence of patients prepared to risk prosecution in order to gain benefit from their medicine is a powerful consideration in the mind of a Pharmaceutical Physician when considering clinical development candidates.



*28 July 1998]**[Continued]*

1.3.1. Smoking not acceptable—It is not generally acceptable in conventional Western therapeutics to require patients to inhale medicine in the form of the products of pyrolysis. The inhaled route does however confer a number of important advantages that present a challenge to replicate through the choice of suitable drug delivery technology and appropriate formulation excipients. See section 5 on Route and Method of Administration.

1.4. Route and Method of Administration Critical—Smoking gives rise to rapid absorption and distribution of unmetabolised constituent compounds, whereas oral administration leads to substantial first pass liver metabolism mainly to the 11 hydroxy forms. Potency of the various metabolites and the time course of their continued absorption, distribution and elimination will give rise to different spectra of beneficial versus adverse effects. Drug delivery technologies can manipulate these differences and generally produce an optimum therapeutic outcome.

1.5. Clinician Support—Notwithstanding the Legal status of Cannabis the practical problems of mounting the clinical trials portion of a development programme are much reduced by the existence of Physicians eager to perform clinical evaluations, experimentation and clinical trials, with large numbers of patients willing to be enrolled in the trials. If placebo trials prove difficult to perform (Ethical objections, difficulty in blinding if active medicine retains psychoactivity) the availability of large numbers of patients willing to participate in the trials programme will permit alternative study designs that usually require greater numbers of subjects.

1.6. Patient Representative Groups—An increasing number of patient groups are expressing support for cannabis based therapy. (Alliance for Cannabis Therapeutics, MS Society, many others internationally)

1.7. Clinical Research Unmet Need—The obvious and understandable lack of enthusiasm by major pharmaceutical companies to include in their R&D programmes a Schedule 1 drug leaves an unmet need. Such need for proper investigation of the therapeutic potential of Cannabis has been identified by many authorities, including, The BMA, The Pain Society, The Pharmaceutical Society, The Department of Health and The Home Office.

1.8. Political Will—Support for Cannabis clinical research has come from Members of Parliament (Austin Mitchell, Dr Brian Iddon), The Lords, The Home Office, The Department of Health. Appendix 2

1.9. Available Literature—Rarely has there been so much written in learned medical publications on the medical benefits of a material which, with the exception of synthetic  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), does not exist as a prescription medicine.

1.9.1. One should view the older literature with some caution though. Much had been published by authors carrying out work for and funded by the National Institute of Drug Abuse (NIDA) in the US. The NIDA has funded research primarily to gain evidence against the use medicinal or otherwise of cannabis. It is not unreasonable to be sceptical about the study conclusions or more precisely the use to which their conclusion have been put. Much of this sort of work has been responsible for seeding misinformation into both the medical and lay literature. The issues of immunosuppression, insanity and deviancy, are good examples of the negative aspects of politically motivated research.

1.10. Value of Anecdote—Equally many reports of beneficial effects are truly anecdotal and there are very few publications on the results of controlled clinical trials. In the pragmatic stage of drug development, however, it is simply untrue to assume that no knowledge can be gained from the literature purely on the basis that the report was anecdotal and not that of a controlled clinical trial. Individual case reports and clinical evaluations of small groups of patients given by experienced clinicians are an extremely useful tool in guiding the emphasis and direction of the early pragmatic stages of clinical development. There exists far more evidence of potential therapeutic benefit of Cannabis than would normally be available on a candidate drug to a Pharmaceutical Physician at the outset of a clinical development programme.

1.11 Mechanism of Action—The discovery of a receptor, identification of metabolic pathways or promising pharmacological models that allow scientists to propose mechanisms of action tends to help legitimise, in medical minds, the potential therapeutic claims made for products where only scant or “unscientific” evidence of efficacy exists. The identification and synthesis of THC, the discovery of CB1 and CB2 cannabinoid receptors in man, and the notion of an endogenous “cannabinoid” anandamide have all helped to elevate the level of the medical and scientific debate about the therapeutic value of cannabis. Such excitement, however, should not cloud the fact that substantial pragmatic empirical clinical research is required to correlate the in vitro and in vivo findings so as to validate the models and eventually the proposed mechanisms of action. In the meantime worthwhile therapy may become available to patients on the basis of demonstrating quality, safety and efficacy of test treatments.

1.12 Causality—Patient reports that document alleviation of symptoms of Multiple Sclerosis following medication with cannabis, the return of symptoms over a thirty day period on withdrawal and alleviation on re-challenge with medication make an elegant illustration of the basic scientific concept of causality.

1.13 Increased Acceptance of Phytomedicines (Plant-Derived)—The consideration of progressing a Cannabis clinical programme is against the backdrop a renewed interest in Phytomedicines. Many large and

28 July 1998]

[Continued]

small pharmaceutical companies now have natural product divisions (Glaxo, Bayer, Fabre). On the whole there are two distinct approaches to developing drugs from plants. The purified single molecule approach or the whole or fractionated extract approach. It is not surprising that most pharmaceutical companies that have over the past few decades honed their skills and experience on and who have gained protection from patenting individual molecules take the former approach. Throughout the world, however there are many large pharmaceutical companies that have successfully developed and registered standardised whole or purified extracts containing a number of the plants' original constituents (Pierre Fabre, Dr Shwabbe, Tsumura, Ipsen). The MCA has been able to provide invaluable advice on specific aspects of the regulatory requirements for standardised whole plant extracts.

1.14 Oral  $\Delta^9$ -THC vs Herbal extract—Many researchers (Musty, Pate, McPartland, Morgan, Notcutt, Grottenhermen) and patients (Randall) note that herbal cannabis is superior to the oral  $\Delta^9$ -THC approved in the US (Marinol) and available in the UK on a named patient basis. The BMA report whilst not giving credence to a whole extract as a medicine nevertheless cites a number of instances where Cannabis was preferred over the synthetic THC. Some say that differences may of course not be related to the therapeutic effects but to patient preference to smoke or for the psychoactive effects. To assume that "patients would say that wouldn't they" introduces unacceptable bias on the commentators behalf especially at the current stage of knowledge. If one assumes the patient and physician observations to be those of improved efficacy and/or diminished unwanted effects then there may be a number of reasons. Indeed if conventional drugs normally given in combination by one route are substituted for a single synthetic molecule given by another route very few physicians would expect the same therapeutic outcome. In pharmaceutical terms oral  $\Delta^9$ -THC can not be expected to be the same as inhaled or oral standardised extracts of Cannabis. The importance of the method and route of administration has already been mentioned. The section below on General Considerations for Pharmaceutical Research and Development Programme goes into greater depth regarding the constituents of Cannabis. However, with the growing awareness of the potential effects of other cannabinoids, terpenes, flavinoids, etc to be found in Cannabis, attaching the beneficial effects to just one component is fast becoming unreliable and certainly requires rigorous clinical assessment in placebo controlled and comparative clinical studies. The prospects of recombining individual purified cannabinoids to mimic the effects of the plant from which they came is daunting in terms of the time and resource that may be required.

1.15 Market Opportunity—If worthwhile medicines can be developed from Cannabis then market need should be sufficient to justify the expenditure on a full scale regulatory programme carried out by small to medium sized development groups. The advantage of a history of safe use and much information of human exposure allows a standardised extracts programme to proceed expeditiously to approval and market. A bottom up reconstitution of a "synthetic cannabis" whilst admirable in purity of concept will be long, difficult and exceedingly expensive, but may be worth pursuing if such an approach proves in time to offer superior therapeutic benefit, additional indications or safe use in more diverse patient populations.

## 2. HOME OFFICE LICENCES

The Home Office has issued to Dr G W Guy licences under the Misuse of Drugs Act 1971, to enable a complete pharmaceutical research and development programme to proceed. The Home Office have stated publicly that in the event of a Product Licence being granted for a medicine containing a Schedule 1 material then such registered pharmaceutical form of that material will be transferred to Schedule 2. The licences will be operated by the UK company GW Pharmaceuticals Ltd. Whilst the licences will also cover all researchers nominated by Dr Guy to participate in the programme, Dr Guy and GW Pharmaceuticals Ltd will remain responsible for the appropriate use of the Cannabis materials and the conduct of the work according to the prescribed schedules of the licences. Two licences have been issued; a Cultivation Licence and a Licence to Possess and Supply for Medical Research.

2.1 Cultivation Licence—This licence permits GW Pharmaceuticals to cultivate from seed or clones a range of Cannabis chemovars (cultivars or races of Cannabis defined by their particular chemical composition) in a highly secure glasshouse facility. GW will work on a scale representative of the quantity of materials required for pharmaceutical batch sizes. Strict Standard Operating Procedures have been agreed to ensure non contamination by chemicals, infestation or fungal growth, consistency of content, methods of harvest, drying, primary extraction, storage, and onward consignment. The Home Office has been most helpful in assisting GW in generating policies regarding, security, controlled drug records, staff health and safety and secure handling of materials that fall under Schedule 1 of the Misuse of Drugs Regulations 1985. Certain materials extracted and purified may in due course need to be covered by Schedule 2 licences.

2.2 Possession and Supply for Medical Research—This licence under Section 7 of The Act which allows Dr Guy and GW Pharmaceuticals to store in a secure facility and dispense Cannabis preparations for the purpose of research was granted after lengthy consultation with the Home Office and they in turn with the Department of Health. GW is grateful to the Home Office in the very helpful way in which these discussions were conducted and the very sound legal and regulatory footing upon which the programme is now based. As additional research and development resource is recruited to carry out the programme the licence will be



28 July 1998]

[Continued

extended to cover those professionals nominated by Dr Guy, and approved by the Home Office, to perform specific sections of the programme. Such professionals will include analytical chemists, formulation pharmacists, Pharmaceutical Qualified Persons, clinical research associates, hospital pharmacists, and clinical investigators. The scale of these operations will be sufficient to allow the acquisition of 500-600 patient years of safety and efficacy data.

### 3. GENERAL CONSIDERATIONS FOR PHARMACEUTICAL RESEARCH AND DEVELOPMENT PROGRAMME

The primary aim of the programme is to produce sufficient evidence of appropriate scope and quality to enable a confident Product Licence Application to be submitted for a pharmaceutical product derived from the Cannabis research programme. The principle categories of evidence that are relied upon by the regulatory authorities are Quality, Safety and Efficacy. The exact techniques and methodological approaches are confidential but the objectives of the programme and the major issues pertaining to the production of evidence are discussed below.

#### 3.1 Objectives

3.1.1 To develop standardised extracts of cannabis sativa specially grown under controlled conditions from plant lines bred to express pre-defined cannabinoid content.

3.1.2 To optimise the route and method of delivery and establish safe therapeutic use in a range of indications.

3.1.3 To provide the materia medica for clinical trials, extended monitoring programmes and commercially following Product Licence Approval by MCA.

3.1.4 To expand the programme internationally with academic researchers and pharmaceutical partners.

3.1.5 To identify, eventually, purified fractions and subset including single entities which have useful therapeutic applications or serve as research tools.

3.2. Desirable Product Characteristics—whilst toxicity of Cannabis is very low and thus the therapeutic index is extremely high (40,000) a number of patients are troubled by the psychoactive effects and in some countries these are deemed to be an unacceptable manifestation of therapy.

3.2.1. Patients have reported that they are able to gain benefit in treatment of symptoms without experiencing untoward psychotropic effects. This may be a consequence of the dose, relative ratios of cannabinoid constituents, route and method of administration or incomplete decarboxylation of the cannabinoid acids during extemporaneous preparation.

3.2.2. Tolerance to the unwanted effects, whilst maintaining a constant beneficial response over time has also been reported.

3.2.3. A product standardised for each of these variables that addresses this “therapeutic window” would in the first instance provide the optimum way of responding to current patient need.

3.2.4. It would appear that the single entity Dronabinol containing synthetic  $\Delta^9$ -THC may not have been optimised for dose and delivery as it is consistently reported that this product produces worse psychotropic effects than herbal cannabis.

3.2.5. The effects of other constituents of the plant (terpenes, flavinoids) may also modify the effects of the “principal” cannabinoids.

3.2.6. Many centuries of safe use of the complete plant with its constituents intact may take a substantial research effort to unravel. It will only be in the very long term that further purification, isolation and recombination of cannabinoids and their incorporation with advanced drug delivery technologies may provide any additional benefit.

3.3. Cannabis constituents—There are over 400 molecules in the cannabis plant 61 of which are unique to the species, the cannabinoids. The word cannabinoid in the medical context is taken to mean the group of mostly  $C_{21}$  compounds. The main structural types are cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD),  $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC),  $\Delta^8$ -tetrahydrocannabinol ( $\Delta^8$ -THC), cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabinodiol (CBND) and cannabitriol (CBO). The postfix A denotes the acid and V (“varin”) denote the propyl analogue.

3.3.1. Content/Potency—It has been said that the potency of Cannabis is increasing and on the face of it an examination of the evidence of THC content of seized materials over the past 25 years (EISOHly et al) would seem to agree with this. What is the more likely situation is that illicit growers have improved their growing, harvesting and preparation techniques. This and the use of modern analytical equipment enable them to produce Cannabis more consistently at the pre-existing higher levels of yield. US seized batches studied between 1977 and 1983 by EISOHly showed  $\Delta^9$ -THC concentrations of up to 14.75 per cent, 14.12 per cent and 13.56 per cent in Sinsemilla, Buds and Loose Marijuana respectively.

28 July 1998]

[Continued

3.3.2. It is now possible by selected breeding techniques to produce plants of predetermined cannabinoid yield with acceptably low intra and inter batch variability. Typical sinsemella  $\Delta^9$ -THC yields of 10–11 per cent can be further augmented both in soil or hydroponically. It is quite understandable that the illicit growers would refine their breeding programmes to yield the highest content of the THC to produce psychoactivity.

3.3.3. Cannabinoid ratios—As the dominant Cannabinoid in most Drug-Cannabis varieties  $\Delta^9$ -THC has also received the most attention from the scientific community.

3.3.3.1. As long ago as 1973 Perez-Reyes and 1974 Karniol et al carried out experiments in humans and showed important effects of CBD and CBN. CBN, a product of THC degradation and not usually present in fresh Cannabis, was 10 times less potent than THC in inducing a “high”. CBD is not psychoactive. It was shown however that CBN and CBD can increase the sedative effects of THC and block the THC induced “high”.

3.3.3.2. Zuardi and Guimaraes have carried out a number of experiments with CBD since the early eighties. CBD administered before THC potentiated the psychotropic effects whereas when administered concomitantly CBD was able to antagonise THC effects.

3.3.3.3. Trouve has shown in isolated heart experiments that CBD can counter the reduction in flow rate and pressure caused by THC.

3.3.3.4. The exact mechanisms of these interactions is not known as CBD does not alter THC blood levels and does not bind effectively to the cannabinoid receptor.

3.3.3.5. The sum of the cannabinoid interactions seen with natural cannabis may yield the beneficial therapeutic effects so often reported. It follows that alterations of the ratios outside those naturally occurring, or omitting some constituents altogether in addition to altering the rate of appearance and distribution of important metabolites through varying the drug delivery technology will give a diverse spectrum of clinical response.

3.3.3.6. Indeed the natural Drug varieties from different parts of the world vary greatly in the THC:CBD ratios. Some are almost pure THC (or THCV) eg Thai, others have more CBD than THC (South Africa, Morocco) but remain drug or intermediate varieties on account of their overall content.

3.3.3.7 This holds true for cannabis resin (hashish) that is normally thought to be predominantly THC but from some regions has been shown to contain equal amounts of THC and CBD. CBD rich varieties often contain significant amounts of CBC, sometimes posing a problem of separation. A Russian weed type plant Cannabis ruderalis contains predominantly CBD. See Appendix 1 on Chemical Phenotype Classifications.

3.3.3.8. It has to be considered also whether CBD is unable to modify THC in THC rich varieties. As growers have moved towards the higher THC levels then the beneficial effects of CBD and/or other cannabinoids may have been compromised.

3.3.3.9. “Reverse Ratio Drug Type” cannabis may show therapeutic promise.

3.3.4. Individual Cannabinoid Activity—CBD alone is sedative and in very high doses is anti-epileptic and anti-psychotic. CBC occurs in high concentrations in certain varieties. The anti-inflammatory properties of THC are exceeded by the more potent prostaglandin E1 inhibitors CBD, CBDA, CBN, CBC and CBG. In addition CBD, CBG, CBC, CBNA have antibacterial and antifungal properties.

3.3.5. Other constituents—McPartland has recently reviewed the activity of other known constituents of Cannabis (in press). He reports that essential oils of Cannabis contain many volatile alcohols, aldehydes and terpenes. Many are lipophilic and possess sedative properties the most potent being linalool, citronellol and alpha-terpineol. Memory loss may be mitigated through the anticholinesterase activity of essential oils. 1,8-cineole increases cerebral blood flow and enhances cortical activity. The increase in cerebral blood flow after cannabis inhalation is not related to plasma THC levels. The flavinoid cannaflavins are equipotent to cannabinoids in Prostaglandin E1 inhibition with the essential oils eugenol, carvacrol and p-vinylphenol being even more potent. McPartland further noted that crude cannabis oil and ethanolic extract inhibit prostaglandins more effectively than individual constituents and suggested synergy. The combined anti-inflammatory and analgesic effects of these other constituents may have important roles in providing clinical benefit in pain management. Comparative clinical trials of whole extracts, subsets and individual components may be very revealing. Some terpenes in Cannabis are also present in *Origanum marjorana* and inhibit many bacteria and fungi. Other terpenes and flavinoids have antiviral activity.

3.4. Clinical Importance—The above information is not only important in designing new medicines derived from cannabis but must be borne in mind when reading any report whatsoever of clinical efficacy. Few, if any, of the studies performed to date with natural cannabis and reported in the scientific literature have made precise evaluations of the actual test materials used. Even an in-depth knowledge of the usual qualitative and quantitative content of cannabis from varying regions or the level of sophistication of growers will not permit a reasonable retrospective estimate of what the patients actually received. The inconsistency of the test medications is probably the single most important factor in the poor reproducibility of the clinical findings of the past 25 years. Under such circumstances review data from individual patients using known single sources can take on a new importance.



28 July 1998]

[Continued]

#### 4. CONSIDERATIONS FOR THE PLANNED RESEARCH TO MEET REGULATORY REQUIREMENTS

Regulatory approval may be given after consideration of the Quality, Safety and Efficacy of a specific pharmaceutical product in question. Approval will therefore be for the product with defined active ingredients, formulation excipients, intended route of administration, agreed indications and dosage advice, final packaging and associated documentation. The approval of a product containing cannabis extract, a cannabinoid or combination of cannabinoids will be for that product only and should not be considered as a general approval for a class of drug or other presentations based on the same active principals.

4.1 Quality—Until the end of the 19th century almost all medicines were of natural (mostly plant) origin. Today, even after the pharmaceutical revolution with the advent of synthetic medicines, more than 25 per cent of drugs in the current pharmacopoeia are of direct or indirect natural origin.

4.2. There has always been interest in the constituents of plants, as the starting point for synthetic activity. There is now renewed interest in drugs from natural sources, either as plant extracts or constituents, particularly in the treatment of diseases which involve immune pathology or cancer. Some prescriptions and plants used in other medical cultures and systems are proving exceptionally useful in diseases which are resistant to the best available (synthetic) Western medicines. Most of these diseases are treated with corticosteroids by default.

4.3. The renewed interest in phytomedicines (medicines based on plant constituents) and herbal medicines (medicines based on plant extracts, not necessarily involving the identification of the chemicals responsible for the benefit) have excited the interest of many pharmaceutical companies.

4.3.1. Glaxo, best known for its brilliant work on synthetic molecules which have been developed into drugs (such as Xantac) has established a natural products division to carry out phytochemical research.

4.3.2. Bristol Meyers Squib has recently introduced Taxotere—a treatment for breast cancer based on Taxol—obtained from the Pacific Yew.

4.3.3. In Continental Europe, major companies such as Schwabe and Ipsen have developed a range of products based on *Ginkgo biloba*, and Lichtwer Pharma has introduced an extract of *Hypericum perforata* under the name Jarsin. The medicinal products produced by these companies are leading pharmaceuticals in European markets, and illustrate the benefits of phytochemical and herbal medicine research.

4.3.4. In the UK Phytopharm has developed a treatment for severe atopic eczema based on a prescription of plants used in traditional Chinese medicine, which is effective in the most severely affected patients who are resistant to steroid treatment.

4.3.5. In France, Pierre Fabre has developed Permixon—an extract of Saw Palmetto for the treatment of benign prostatic hypertrophy. In clinical trials this product performed as well as finasteride—a product based on a synthetic molecule.

4.3.6. Japanese companies such as Tsumura have based their major pharmaceutical research efforts in phytochemistry.

4.3.7. A new generation of specialist phytochemical companies is emerging (Shaman Inc, Xenova Discovery Ltd etc.). The raison d'être of these companies is to discover new medicines from the plant kingdom.

4.4 During the period when synthetic medicines were regarded as the prime focus of the pharmaceutical industry, regulatory procedures grew up around synthetic molecules. In the case of phytomedicines and herbal medicines, where the active ingredient has not yet been identified, this poses problems for the standard regulatory model. The principal concerns of regulatory authorities are quality, safety and efficacy but the emphasis on these components may be different. In the case of synthetic medicines there is a long build-up of experimental work to establish that a chemical is safe enough to be used in humans for the treatment of disease. In the case of traditional medicines the starting point is a presumption of safety and efficacy based on traditional use. In the case of phytomedicines and herbal medicines control of quality is paramount, but involves a broader range of disciplines than in the case of synthetic medicines.

4.5. Control of starting materials is very important for natural products. Where a pharmacopoeial monograph exists for the plant material this deals with identification of plant species, its accurate botanical description and its organoleptic characteristics. Increasingly, the regulatory authorities are expecting applicants for Marketing Authorisations to show that they have control over the horticultural factors which influence quality of growing materials, the processes of harvesting and primary manufacture. This establishes the pattern for regulation of the quality of the starting materials. In the case of *Cannabis sativa*, there is an opportunity to provide detailed information on the genetic make-up of the plant strains and it is possible to select strains which exhibit a particular make-up of constituents.

4.6. Generally, there are a number of well established pharmacopoeial tests for the quality of plant materials, and the applicant needs to build on this basic framework in order to demonstrate control over the variations in composition which are a consequence of its natural origin. Some of the regulatory procedures which are applicable to natural products and of particular relevance to quality control of *Cannabis sativa* are

28 July 1998]

[Continued

illustrated by three products of natural origin, demonstrating the way in which regulatory control is organised, particularly with respect to quality.

4.6.1. Gentamicin—Gentamicin sulphate is an aminoglycoside antibiotic produced by a micro-organism. It is the subject of a monograph in the current BP and other major pharmacopoeias. Gentamicin sulphate is a complex mixture of compounds which have similar antibiotic activity, and which are identified and quantified by high performance liquid chromatography (HPLC). It is believed that more than one Gentamicin sulphate contributes to the overall efficacy of the product and the activity of the official preparation is defined by reference to its overall biological activity, with limits on the amounts of specific Gentamicin sulphates in the mixture.

4.6.2. Papaveretum—In 1806 Sertürner isolated morphine from opium, and this may be regarded as the starting point for phytochemistry. Since then, preparations of morphine have been developed and are found in most pharmacopoeias. Regulatory control has been directed towards the definition of physico-chemical parameters which provide assurance on quality of the active ingredient—morphine. However, in the case of opium a preparation of mixed alkaloids has been in use as an alternative to morphine preparations to the present day. Many physicians believe that papaveretum provides a better quality of pain relief than does morphine. Papaveretum contains morphine hydrochloride and other opium alkaloids including codeine and papaverine. So useful was this preparation that despite the undesirable effects of one of the minor alkaloids—noscapine, the preparation has been reformulated based on a mixture of morphine, codeine and papaverine. It still remains in use as an analgesic. The regulatory history of papaveretum illustrates the consideration which needs to be given to subjective criteria in assessment of clinical benefit. Morphine is clearly an analgesic component of opium which can be used by itself. However, patients achieve better quality of pain relief from the same amount of morphine when it is given in combination with other components of opium. This synergy between components is characteristic of natural products, and is believed to operate in the case of cannabis.

4.6.3. Digitalis—The need for a broad regulatory approach is illustrated by the example of digitalis. The current pharmacopoeia contains a number of medicines based on digitalis. It is 200 years since William Withering described the use of digitalis leaf in the treatment of “dropsy”. This preparation is still in the current pharmacopoeia. Digitalis leaf is standardised in terms of glycosides and the pure compound is also the active ingredient in another pharmacopoeial preparation—digoxin tablets. In the case of digitalis regulation of quality is carried out using physicochemical tests. The development of tests which provide assurance on quality takes time and the history of registration of digitalis preparations provides a useful framework for the type of test which is required in the regulation of other medicinal products.

4.6.4. These examples could be multiplied, but the examples given show the way in which regulatory control, particularly in respect of quality can be exercised in the case of natural medicines. In the case of products based on *Cannabis sativa* it is possible to show a chain of control from the selection of the plant, control of the production of the active ingredient by manipulation of horticultural conditions, and assay of constituents using state-of-the-art physicochemical methods through to a conventional Finished Product Specification. These quality control criteria ensure that a defined product can be used in clinical trials intended to show the clinical benefits of this medicine in the treatment of diseases which are refractory to the best available synthetic medicine.

4.7. The research to date indicates that, although the constituents of Cannabis have been identified, the use of single chemicals may not produce the quality of relief produced by an extract of the whole plant. Reference to experience with papaveretum shows that this approach is not without precedent.

4.8. The recognition by regulatory authorities that heterogenous botanical medicine (US terminology) and medicinal herbs (European term) may have properties which are greater than the sum of the parts. This has prompted a rethink on the part of regulatory authorities to the control of these agents. Phytomedicine and herbal medicine companies are in an active discussion with the regulatory authorities to provide assurance on appropriate control procedures for these medicines.

4.9. G W Pharmaceuticals Ltd is well equipped to lead in this dialogue with the regulatory authorities.

4.10. Safety—When planning a pharmaceutical regulatory R&D programme it is important to include in the trials evaluations and assessment of end points designed to address known or suspected adverse or unwanted effects of the last intervention. Such knowledge is usually gained from pre-clinical and earlier clinical reports generated internally by the company concerned. In the case of cannabis much is available from the literature and personal communications. In prioritising for patient safety and efficient research effort it is important to make clear judgements of the relative importance and validity of the various claims of adverse effects associated with cannabis therapy. Notwithstanding the previous observation that little is known of the exact composition of the materials administered to patients the total exposure to all chemovars of natural cannabis provides a working envelop of safety. Again it is important to stress that the inherent human toxicity of cannabis is so low that there have been no audited reported cases of death from administration of cannabis for medical nor recreational purposes. Provided products that are developed are representative of and fall within and the existing broad range of cannabis chemovars then certain reliance can be placed on this observation. Such low toxicity cannot be automatically assured for single synthetic molecules known to exist in the whole plant.



28 July 1998]

[Continued

4.10.1. Grinspoon and Bakalar pointed out that by comparison to almost all available prescription medicines Cannabis has remarkably low toxicity and that one of marihuana's greatest advantages is its remarkable safety. They also considered Marihuana as "far less addictive and far less subject to abuse than many drugs now (1995) used as muscle relaxants, hypnotics, and analgesics.

4.10.2. Therapeutic index—A ratio of lethal to effective dose of 40,000 to 1 for cannabis compares with approximately 10 to 1 for alcohol, 25 to 1 for aspirin and 50 to 1 for morphine.

4.10.3. Zimmer and Morgan—cite more than a dozen papers with a similar view.

4.10.4. Lung Disease—The greatest area of concern has been the effect of smoking on the lungs. The picture however differs from tobacco smoking and authors differ on the relative risks.

4.10.4.1. Although higher in tar and other carcinogens per cigarette the total exposure to patients is likely to be less with cannabis. Furthermore, unlike heavy tobacco smokers, heavy marihuana smokers exhibit no obstruction of the small airways and after ten years of study Tashkin reported that "marijuana smokers probably will not develop emphysema." Much of the US work in this area used standard cigarettes prepared with cannabis grown by the Research Institute of Pharmaceutical Sciences at the University of Mississippi for the NIDA. Their Mexican variety in the early days contained 1–2 per cent THC. Patients had reported that they need to smoke more of these low dose cigarettes to obtain satisfactory relief with a concomitant increased exposure to inhaled smoke. More recently the THC content of these materials has increased to 2–4 per cent.

4.10.4.2.—The risks associated with fungal infection (*Aspergillus*), microbial contamination, exposure to pesticides, fungicides and heavy metals are removed by adoption of modern methods of cultivation of medicinal plants. This and strict quality control procedures mean that opportunist infections in patients arising from the medication are not an expected sequelae of standardised therapy.

4.10.4.3. Although it is reasonable to attribute potential lung disease to the inhalation of products of pyrolysis it is equally important to consider the effects on the lung and systemically when mimicking this route with vaporisers, nebulisers or dry powder inhalers or metered dose inhalers.

4.10.5. Dependence/Tolerance/Addiction—Most authors now agree that dependence and addiction are not likely to be a troublesome feature of the therapeutic uses of cannabis. Any such risk that may exist is likely to be further reduced by the application of drug delivery technologies and appropriate dosage. This was certainly the case with Controlled release oral morphine. Although tolerance has been noted to certain unwanted effects many patients report continued relief over long periods on the same "dose" of cannabis. Long term studies and monitored follow up of all trial patients should provide appropriate information.

4.10.5.1. When patients have received benefit in clinical trials it is conventional for the sponsor to provide continuing supplies of test medication for use under the doctor's supervision, on a compassionate basis. During this period of compassionate supply which is done under the "Specials" provisions of the Medicines Act (1968) and subsequent Statutory Instruments, additional safety information can be obtained. It is possible, for example, for the sponsor of the clinical trial to make detailed reporting of benefits and adverse events to the sponsor, a condition of re-supply. The comfort gained from these observations is especially important as it provides information on use in a larger population of patients. Upon completion of a trial patients will not, under the Home Office Licence, be able to receive further supplies of the test medication from their doctor on a compassionate basis.

4.10.6. Gateway Theory—It is not accepted that the exposure of patients to therapeutic doses of Cannabis extract, cannabinoid combinations or single cannabinoids will lead to patients seeking to obtain "hard drugs". This has not been a problem with the modern use of Morphine. Strong arguments have been made for over thirty years that cannabis is a "stepping stone" to hard drugs (Heroin in the 60s, LSD in the 70s and currently cocaine). Cannabis is the fourth most popular drug of abuse after caffeine, alcohol and nicotine. Users of less popular "hard" drugs are also likely to have used the more popular ones. What has been described is a statistical association between the two activities, not one leading to the other. Long term follow up of patients will again provide pertinent information.

4.10.7. Immunosuppression—Nahas published his work in 1974 and 1976 where he exposed human lymphocytes (T-cells) that had been extracted from cannabis users and nonusers to known immune activators and measured their rate of transformation. He showed diminished immune response in cells from cannabis users which he concluded weakened their immune system and made them susceptible to infection. Using the same techniques other scientists have consistently found no difference in the transformation in T-cells from users and nonusers. THC has been shown to produce immune impairment in animals but only at doses 40 to 1,000 times the psychoactive dose. The BMA report says "A prospective study failed to find any relationship between cannabis use and rate of development of clinical AIDS in HIV-positive men (Kaslow et al, 1989)" Mathre points out that "... starvation and malnutrition are themselves significantly immunosuppressive, much more so than any suppressive effects ascribed to cannabis."

4.10.7.1. The FDA has approved the use of  $\Delta^9$ -THC in AIDS wasting syndrome.

4.10.7.2. The usefulness of cannabis and THC in AIDS management clearly requires further investigation since there are conflicting results in this area. In any trials carried out in the management of AIDS-related

*28 July 1998]**[Continued]*

disease syndrome, markers of immune function would be built into the study design. It would be appropriate to discuss such studies with the MRC HIV Clinical Trials Centre when framing the plans for an eventual clinical study.

4.10.8. Wootton report—In 1968 the report of the Wootton Committee, set up by the UK Government to advise on cannabis, was published. The committee found no evidence that cannabis led to crime or aggressive behaviour, nor that it produced psychotic states in otherwise normal users. The report concluded: "Having reviewed all the material available to us, we are in agreement with conclusions reached by the India Hemp Drugs Commission and the American La Guardia report that the long term consumption of cannabis in moderate doses has no harmful effects".

4.11. Efficacy—The principal aim of the clinical development programme will be to carry out a range of clinical trials of size, scope and quality sufficient to support a product licence application to the MCA for given indications. Whilst care will be taken to avoid the "panacea" approach the programme will recognise the current strength of medical opinion in favour of a range of indications. Trials will in the first instance focus on:

4.11.1.1. Symptom control in patients with Multiple Sclerosis.

4.11.1.2. Weight loss in Aids Wasting Syndrome.

4.11.1.3. Intractable pain failing to respond to conventional therapy under to stewardship of pain clinic specialists.

4.11.2. The classical approach to clinical development would usually follow the time honoured route of Phases I—III trials in the pre-marketing period and Phase IV thereafter on approved indications and further phase II and III to explore wider uses or different sub-groups of responders. One may also revisit Phase I in the event of changing the dosage form and/or route of administration or if the therapy is to be extended to a broader patient population ie women, children or the elderly or if more prolonged dosage regimen than initially approved required.

4.11.3. GW's experience of ethno-botanical or vernacular medicines is that, although not subject to the rigorous standards of modern pharmaceutical development, much information can be gleaned on the safety and efficacy of the materia medica in the dosage forms used and as administered by the practitioners of such medicines. Indeed the medical literature contains hundreds of papers on the therapeutic uses of *C. Sativa* its tinctures and extracts. Such knowledge has in the recent past allowed Dr Guy in the UK to progress clinical trials on other plant based medicines into Phase II earlier than would otherwise be the case for a New Chemical Entity or indeed a highly purified single chemical extracted from a plant or biological source.

4.11.4. One of the most important roles of the clinician is to balance the risk of a potential medical treatment against the benefits to be gained from its use. Based on the extensive information extant on the toxicity of Cannabis and some of its constituents including formal rodent toxicology studies performed by US Government agencies and on the very nature of the medicines to be tested Dr Guy intends to carry out the vast majority of the work in patients as opposed to commencing with volunteers. The risk benefit ratio in patients suffering with Multiple Sclerosis or AIDS will certainly be more preferable than that of healthy volunteers who may well include young students or other impressionable groups.

4.11.5. A group of principal investigators is being assembled with the first in place at the time of this evidence. In general investigators will have already worked with patients who have been exposed to cannabis based therapy, and who have direct experience in clinical trials methodology and procedure in this particular field. There are efforts underway to evolve suitable clinical protocols for the evaluation of Cannabis in a variety of indications.

4.11.6. In addition to the active clinical trials investigators the programme benefits from a panel of advisors that cover the wide range of disciplines pertinent to this development programme including pharmacognosy, pharmacology, biochemistry, toxicology, statistics, clinical trials, pain management, Multiple Sclerosis and AIDS.

4.12. Special objectives of the Clinical Development Programme—Details of the trials programme will remain confidential, however, the objectives and certain considerations are listed below.

4.12.1. Tolerability and Safety—The evaluation and monitoring of the safety of all candidate test articles will be paramount throughout all phases of the developments. In view of current knowledge of the low toxicity of whole cannabis extracts and indeed their prescription by clinicians until 1971 early studies will use such total extracts and will generally commence in patients with the target indications as opposed to volunteers. As fractionation of extracts occur or if specific extracted molecules are to be used then the threshold of suspicion regarding implied safety should be lowered. This will involve specific pre-clinical toxicology studies and Phase I first dose in man protocols that may well require the recruitment of healthy volunteers.

4.12.1.1. Specific emphasis will be placed in these early Phase IIa studies on monitoring as would be found more usually in Phase I. In addition to regular observations and clinical biochemistry specific attention will be paid to the appearance of tachycardia increased supine blood pressure and orthostatic hypotension.



*28 July 1998]**[Continued]*

Investigators will be encouraged to include in their protocols evaluations of psychopathological and psychometric parameters, including mood, memory, motor co-ordination, cognition, time sense and self-perception.

4.12.2. Pharmacodynamics—The many permutations of delivery and active constituent of the extracts will need to be evaluated both empirically in proven clinical models and through specific pharmacokinetic and pharmacodynamic studies. Much of the early Phase IIa work will prepare the ground for the later controlled studies by finessing the clinical models to a point of reasonable discernment between candidate interventions. Phase I studies including in some cases health volunteers will be an ongoing feature throughout this development.

4.12.3. Psychomotor Performance—Zimmer and Morgan report that, in driving studies, cannabis produces little or no car-handling impairment—consistently less than that produced by low to moderate doses of alcohol and many legal medications. Patients will, however, be advised appropriately not to drive nor operate machinery whilst on medication.

4.12.4. Patient Exclusions—Certain patient groups will be excluded from studies until sufficient safety data is available ie pregnant or lactating mothers, women who may become pregnant within six months of taking the test articles.

4.12.5. Assessment of various routes and methods of administration—In addition to the potency and relative constitution of the plant and its standardised extracts the absorption, distribution, metabolism and elimination of cannabis depends on the method and route of administration. Oral bioavailability is reported at about 10 per cent due to hepatic first pass but will also depend on the effectiveness of the dosage form. The resultant circulating metabolites, their time course of distribution and elimination, and thus the clinical effects will therefore vary dependent upon the drug delivery modality utilised. Furthermore the opportunity to divorce the unwanted effects from the beneficial effects may become achievable by the correct choice of the dosage form, route and frequency of administration.

4.12.6. Earlier Clinical experiments on candidate test articles—The initial studies by the principle investigators will be small to medium sized (20-50 subjects), open pragmatic clinical experiments using the patients as their own control (n of 1 design). Special emphasis on safety monitoring will complement the other study objectives of assessing beneficial effects as reported by the patient and as observed and deduced by the investigator. Objective measures will be made where appropriate in these pilot studies.

4.12.7. Dose Ranging—The overall safety profile gleaned from literature, vernacular use and direct clinical experience suggests that dose ranging will be possible by escalating dose methods in the earliest studies. Specific dosage recommendations would be preferred for later studies and indeed general clinical use but as with the clinical use of Morphine individual patient titration may be deemed necessary in the initial clinical experience. Thereafter more general dosage recommendations may be advised to the prescriber.

4.12.8. Placebo Controlled Trials and Blinding—From the wide variety of evaluation end points considered in these studies those that are sensitive and specific to the interventions will emerge. Such favoured end points will form the foundation of the evaluations of efficacy in the later comparative and/or placebo controlled trials. It is fully recognised that Ethics Committees may not favour placebo controlled trials in certain indications in view of the availability of alternative medications or satisfactory prior evidence of efficacy. If the candidate test medications selected exhibit at the target doses psychoactivity then blinding may be an impractical proposition.

4.12.9. Comparative studies—The existence of an approved synthetic oral preparations of  $\Delta^9$ -tetrahydrocannabinol (Marinol) and Nabilone under Schedule 2 allow the opportunity to carry out comparative studies of test articles to the existing products. In Germany Dr Gorter is planning a 360 patient placebo controlled, double blind, parallel group trial in AIDS Wasting Syndrome comparing THC, Herbal Cannabis extracts and placebo.

4.12.10. Larger Scale Controlled Clinical Trials—Phase III clinical trials will be largely descriptive. Classical comparative, control groups and open design will be undertaken in large groups (100-300 patients). The MCA has in connection with other development programmes accepted the value of larger scale open or control group studies in evaluating efficacy and safety. Controlled trials will include multi-centric and multiple centred pooled designs. Each indication sought for regulatory approval should be tested in separate studies though safety data may be pooled across indications.

4.12.11. Identification of subgroups of responders—will form later stages of the development but may be brought forward if there is inconsistency of response in chosen patient groups or stratified responses are seen in the earlier studies.

4.12.12. Long Term follow-up and patient safety monitoring—The pivotal regulatory programme will aim to achieve 500-600 patient years of closely monitored data. As a chosen candidate product (content and delivery) progresses into more advanced clinical trials it will be important to continue to monitor all patients that agree to continue on treatment to provide long term safety and efficacy data. This has been achieved in similar development programmes by instituting specific trials continuation programmes. The continuation periods allow further refinement of therapeutic regimen in terms of posology, frequency and route of

*28 July 1998]**[Continued]*

administration. The large amount of such data available over periods of continued exposure to the test articles provides extremely valuable accompanying reference data in support of Product Licence Application. Agreement by the investigator and the patient to comply with this extended data collection may be a condition of entry into certain parts of the programme.

4.13. Continuation supplies—If the test medication is demonstrated in certain individual patients to be beneficial, there is a risk that abrupt withdrawal of treatment at the end of the initial study period may leave the patient seeking continued benefit through acquisition of street cannabis. The Home Office Licence does not permit compassionate supply thus all patients receiving the test articles will do so only as part of monitored approved prospective clinical studies.

4.14. Protocol development, Medico-legal considerations—The initial protocols will be prepared by the investigators and remain mainly in their own style and structure. In due course a standardised protocol structure agreed by the appropriate interested parties will be adopted. Ethics Committee approval will be obtained for each study and re-submissions or notifications will be made as required in the event of protocol amendments and centre extensions.

4.15. Regulatory responsibility—will remain with the investigators for the initial studies under DDx but Dr Guy intends to compile CTXs for further studies as soon as the appropriate data is available in the correct format.

4.16. Insurance—A no fault compensation insurance scheme will be put in place and each investigator will be able to draw cover from an umbrella policy. The current no fault schemes available in London also provide an element of product liability for the test articles.

4.17. GCP—The spirit and objectives of Good Clinical Practice will be recognised from the outset and more rigorously enforced as the programme progresses into the more formal pivotal studies. At this point further DDx studies will be inappropriate on the candidate test articles for the chosen indications and CTX will be sought for further trials.

4.18. Ethics—An initial clinical efficacy trial protocol falling under the Phase IIa category has already received Ethics Committee approval. The investigator will be Dr William Notcutt, a pain specialist and one who has considerable experience with patients resorting to self medication with cannabis. In view of the greater scope of the overall programme now possible under the Home Office Licence Dr Notcutt has now sought the support of colleague Pain Specialists, to refine some of the detailed points of the protocol. Any changes made prior to commencement will be notified to the Ethics Committee by way of a Protocol Amendment. Dr Notcutt will also seek regulatory approval by way of a DDx from the MCA.

## 5. ROUTE AND METHOD OF ADMINISTRATION

After the quantitative definition of its principal constituents the method and route of administration will be the most important factor to affect the therapeutic value of Cannabis. There are several variables which affect the choice of constituents, dose and route of administration. Smoking is clearly an effective route of administration, but is socially and medically undesirable. It is one objective of the R&D programme to devise and develop methods of insufflation and inhalation which do not involve smoking, but which deliver cannabinoids in decarboxylated form to the oropharynx and lungs.

5.1. Variable bioavailability—It has often been said that the rate and extent of absorption of the active cannabinoids is highly variable and when given orally is low. This in itself may not be so problematic as many very successful drugs today (eg Nifedipine, Morphine) display blood level variability and/or low bioavailability of the same order as may be seen in the limited pharmacokinetic data available on cannabis.

5.2. Smoking—gives rise to rapid absorption of constituent compounds that enter the bloodstream and reach the brain mainly unmetabolised within 15 minutes. Smoking of cannabis creates and extemporaneous chemical step (decarboxylation), vaporisation of the cannabinoids and essential oils which are then absorbed through the mucosa of the oropharynx and through the lungs. The rate and extent of absorption will depend upon the smoking technique and will vary between the various constituents, so to will the corresponding appearance and distribution of their metabolites. Whilst smoking is an unacceptable method it does, as mentioned above, offer some pharmacokinetic and pharmacodynamic advantages that will prove difficult to replicate with advanced drug delivery technology. These advantages include:

5.2.1. Potency assessment—The varying psychotropic potency of street cannabis is well understood and covered elsewhere in this evidence. The extremely rapid absorption and distribution of essentially unmetabolised parent compounds following inhalation allows the subject to assess the potency of the material and moderate his consumption accordingly.



*28 July 1998]**[Continued]*

5.2.2. Decarboxylation—The principal cannabinoid acids THCA, CBDA, CBGA, CBCA and CBNA require decarboxylation to be psychoactive. Although some decarboxylation occurs during the post harvest drying along with terpene isomerisation to polyterpenes, it is generally achieved when cannabis is heated above 110-120 degrees C. Such temperatures occur in the super heated air stream behind the ember when cannabis is smoked in certain cooked recipes ie brownies, shortbread. Researchers have also questioned whether the oral carboxylic acids are entirely inert. One paper has shown that THC acid is 20-50 per cent as effective as the decarboxylated form in I.P. injection doses used to study anticonvulsant activity and motor performance of cannabinoids in mice (Karler and Tukanis, 1979. NIDA Res. Monogr. 79: 96-107). Also decarboxylation might occur in the GI tract to some extent.

5.2.3. Possible Therapeutic Window—Patients have reported that they are able to obtain symptom relief without being unduly troubled by psychotropic effects. This “therapeutic window” may arise not purely from the blood levels achieved or remaining in an appropriate range but also from the time course of the event. The rate of change of blood levels and the rate and extent of appearance of circulating metabolites of the respective active components will have a marked affect on the occurrence, and the patient perception, of adverse effects. All these parameters are liable to change when switching routes and methods of administration.

5.2.4. Self/Auto Titration—Inhalation of rapidly absorbed drug permits patients to titrate the dose consumed to their exact needs. A picture is emerging that patients seeking pain relief may, as in the case of Morphine, require individual dosage titration. In addition patients report that as their symptoms vary in type and intensity, their dosage requirements are not the same from episode to episode. Patient controlled analgesia is an example of how current clinical practice addresses this variable requirement. The requirement for individual titration may not necessarily rule out the possibility of standard dosage regimen, but as with Morphine experience will need to be gained over time to allow exact advice to be given to the prescriber.

5.3. Inhaled Route—Technologies will be applied to provide absorption via the lung and the oropharyngeal mucosa.

5.4. Oral Route—Studies to date via the oral route have used very basic dosage forms (soft gelatin capsules and sesame oil) which would not be expected to confer any control of delivery. It is probable that the opportunity to achieve blood levels within a therapeutic window has been missed. The immediate absorption of drug will give rise to early appearance of relatively high levels of the more psychoactive 11-hydroxy metabolites of  $\Delta^9$ -THC. Although not optimum at present, with better knowledge of the desired pharmacokinetics of the principal cannabinoids controlled release oral products may well prove, in future, to be very useful.

5.5. Other methods—Skin patches, transmucosal delivery, suppositories and ophthalmic delivery technologies will offer opportunities to optimise the rate and extent of absorption, avoid first pass, control the type and rate of appearance of metabolites and give the physician and/or patient the ability to tailor their medication for their exact therapeutic needs.

## 6. CONCLUSION

Under normal circumstances, development of a synthetic new drug is expensive, lengthy and risky. Many pre-clinical tests need to be carried out before testing in man can be justified, and this is expensive in terms of time and effort. There is no guarantee that drugs found to be effective in the laboratory will be useful in man. This risk of failure is greatest during the pre-clinical phase, and although it is less when a compound reaches the stage of clinical testing it is still significant.

For a drug based on a natural product which has a history of use in man there is a presumption of safety and efficacy, and this knowledge reduces the risk of failure and the time to reach the clinic.

Patients will be served best by the timely introduction of pharmaceutical quality standardised extracts of cannabis in which safety and efficacy has been satisfactorily demonstrated in controlled clinical trials. The longer term endeavour to isolate individual cannabinoids and establish their therapeutic value individually or in combination may also have merit.

28 July 1998]

[Continued

*Acknowledgements*

Linda Anderson  
 Robert Clarke  
 Paul Consroe  
 Mahmoud ElSohly  
 Franjo Grottenherman  
 Clare Hodges  
 William Notcutt  
 John McPartland  
 Raphael Mechoulam  
 Eteine De Meijer  
 Dave Pate  
 Roger Pertwee  
 Amala Raman  
 Patrick Wall  
 David Watson  
 Brian Whittle

I am grateful to the above for the time and effort they have contributed in assisting me during the compilation of this evidence.

## GLOSSARY OF TERMS AND ABBREVIATIONS

**Cannabis**—The plant *Cannabis sativa* L, this commonly refers to all varieties of drug cannabis. Other authors recognise *C. ruderalis* and *C. indica*. Also known as Marijuana, Marihuana (US, Mexico), dagga (Africa), ganja (India).

**Cannabinoid**—group of chemicals unique to the cannabis plant abbreviations are as follows:

|                 |                              |
|-----------------|------------------------------|
| CBC             | cannabichromene              |
| CBD             | cannabidiol                  |
| CBG             | cannabigerol                 |
| CBE             | cannabielsoin                |
| CBL             | cannabicyclol                |
| CGN             | cannabinol                   |
| CBND            | cannabinodiol                |
| CBO             | cannabitriol                 |
| $\Delta^8$ -THC | delta-8-tetrahydrocannabinol |
| $\Delta^9$ -THC | delta-9-tetrahydrocannabinol |
| Post fix-A      | denotes acid                 |
| Post fix-V      | denotes propyl anologue      |

**Hashish**—a drug formed of resin heads of glandular trichomes shaken or rubbed from floral clusters. May be extracted with solvents to produce hashish oil.

**Buds**—cannabis in the form of flowering tops with seeds.

**Sinsemilla**—cannabis in the form of flowering tops of female plant with no seeds.

**Loose marijuana**—cannabis plant material with leaves, stems, and seeds.

**Phenotype**—outwardly measurable characteristics of an organism determined by the interaction of the individual genotype with the environment.

**Chemotype**—a specific chemical phenotype which in Cannabis is usually based on ratios of cannabinoids.

**Chemovar**—cultivars of races of Cannabis defined by their particular chemical composition.



28 July 1998]

[Continued

## Appendix 1

Chemical Phenotype Classifications of Cannabis—according to Small & Beckstead (1973) and Fournier & Paris (1979).

| <i>Phenotypes</i>         | <i>[THC]%</i>         | <i>[CBD]%</i>         | <i>[THC]/[CBD]</i> |
|---------------------------|-----------------------|-----------------------|--------------------|
| Small & Beckstead         |                       |                       |                    |
| —Drug                     | > 0.3 (in both sexes) | < 0.5 (in both sexes) | —                  |
| —Intermediate             | > 0.3 (in females)    | > 0.5 (in both sexes) | —                  |
| —Non-drug                 | < 0.3 (in females)    | > 0.5 (in both sexes) | —                  |
| Fournier & Paris          |                       |                       |                    |
| —Fibre Hemp               | < 0.5                 | > 0.5                 | < 1                |
| —Resinous <i>Cannabis</i> | > 0.5                 | < 0.5                 | > 1                |

## Appendix 2

## POLITICAL SUPPORT

## Cannabis-based Medicine

20 April 1998

Lord Lester of Herne Hill asked Her Majesty's Government:

"Whether they will introduce an amendment to the criminal law to permit the use of cannabis for palliative care of the terminally ill as part of a prescribed course of medical treatment." [HL 1427]

Lord Williams of Mostyn: If and when the benefits of a cannabis-based medicine are scientifically demonstrated and a marketing authorisation issued by the Medicines Control Agency (MCA), the Government would be willing to propose amendment of the misuse of drugs legislation to allow the prescription of such a medicine. It would not be right to amend the misuse of drugs legislation to allow the prescription of a cannabis-based medicine, or any other potential medicine, unless or until its quality, efficacy and safety have been established.

House of Commons Written answer 5 May 1998.

## Cannabis

Mr Gordon Prentice: To ask the Secretary of State for Health if he will make a statement on the meeting held on 10 March between the Chief Medical Officer and departmental officials and the BMA called to discuss the report on the therapeutic uses of cannabis. [40008]

Mr Boateng: The Chief Medical Officer met British Medical Association representatives to discuss future action on the BMA report "Therapeutic Uses of Cannabis" on 10 March. There was agreement on the importance of encouraging research on cannabinoids because of the potential benefits for people with multiple sclerosis and those with chronic pain, especially during terminal care. Research could take place within existing legislation and the Chief Medical Officer confirmed that the Home Office and Medicines Control Agency are prepared to look sympathetically at bona fide research proposals.

June 1998

## Examination of Witness

DR GEOFFREY GUY was called in and examined.

## Chairman

690. Good morning, Dr Guy. Thank you very much for coming to talk to us. Could you tell us something about yourself and how you came to be interested in the question of the therapeutic uses of cannabis?

(Dr Guy) Yes, indeed, my Lord Chairman. I am a pharmaceutical physician. I have been working with the pharmaceutical industry for about 18 years. My involvement over that 18 years started with taking new chemical entities from the laboratory to the first dose in man and then the early studies of these new

chemical entities, and moved on to biotechnology products. At the same time I was involved with plant medicines, as I was working for a French pharmaceutical company. In the more recent years I was responsible for founding two research companies, one researching drug delivery methods and technologies, which brought about a dozen products to the market in 30 markets in the world, and also a medicines company responsible for developing plant medicines from traditional Chinese medicines in the first instance. The reason I became interested in cannabis is that in our drug delivery work I had carried out a lot of work with morphine

28 July 1998]

DR GEOFFREY GUY

[Continued]

Chairman *contd.*]

and did some of the initial work on controlled release morphine tablets. By about five years ago I had identified cannabis as another candidate that may benefit, either in the single form of tetrahydrocannabinol or complete cannabis, from improved drug delivery. At that time I was thinking of a skin patch. My initial inquiries—and they were very, very superficial through my own technical staff to the Home Office, with whom we had an on-going relationship, through our controlled drug licences—indicated that the way forward at that time would be fraught with bureaucratic and other difficulties. So, like I think many other pharmaceutical companies, I turned my attention to other projects at the time. Last year my attention was drawn to the meeting of the Royal Pharmaceutical Society looking at the therapeutic uses of cannabinoids. I attended that meeting to see how the state of this science was and realised that there had been a number of changes not only in the number of clinicians interested in the area but more information coming through from patients using materials in society. Also, there seemed to be a softening of the Government approach to these materials. At the end of that meeting I was invited to attend a Parliamentary delegation last year to visit the Home Office with a group from ACT and a number of clinicians (ACT is the Alliance on Cannabis Therapeutics). We discussed with Paul Boateng, the Chief Medical Officer and other officials the possibilities of transferring cannabis from Schedule 1 to Schedule 2 to facilitate the research. We were told there was no political will at that time to do that, but we were encouraged to discuss the matter again at the Home Office. The Home Office had, at that time, issued about 19 licences. I went to see the Home Office a week later and laid out a plan for the complete development of a pharmaceutical form of cannabis and I submitted my licence application in January of this year.

691. Can you tell us about the developments since you wrote your paper?

A. Essentially there are two major areas of development. One is in the science and the understanding of what is going on (I wrote that paper a couple of months ago and a lot of things are changing very rapidly) and the other one is in the practical issues. In relation to the practical issues, we anticipate, under our cultivation licence, to commence planting cannabis within the next few weeks. We would anticipate, therefore, after a 14-18 week growing cycle (in the first instance 18 weeks), we would have our first materials available for extraction at laboratory grade. We are, at present, working up a number of analytical methods for those materials so that we can follow the growth of the plants each week through their cultivation. Those laboratory materials will be tested, analysed and will be available for incorporation in prototype formulations early next year. We will be running a number of activities in parallel at that time, but essentially those activities will be activities to support a confident move into human clinical research with prototype formulations. I would hope we would be close to that by this time next year.

Lord Nathan

692. I wonder whether the cannabis plants would be grown from seed or cloned?

A. Essentially, in the fullness of time, we must grow from clones. However, our partners in Holland, who are experts in growing and breeding medicinal varieties or chemovars of cannabis, have been unable (and it seems they will still be unable) to obtain the appropriate export licence to export plants, and a clone is deemed to be a plant in Dutch law. Whereas there is no prohibition on the movement of seeds, the Dutch authorities have rather dug their heels in. Unfortunately, instead of being able to set off straight away with their clones, which have been established over many years, of which we know their content and we know the purity of the breed because of their breeding capabilities, we will have to bring in seeds. They have a number of seed lines that have been bred for purity of seed line over five or six generations, but that does mean that we will have to start off breeding from seeds; breeding males and females, culling off the males and then cloning from the females. It will cost us time.

Lord Dixon-Smith

693. We had a session with some Dutch people and it is quite clear, of course, that although the use of cannabis is tolerated in Holland, those who dispense it actually have to go through an illegal route in order to purchase it. So there must be a fairly strong regulatory regime if the Dutch are growing this and experimenting with it. Is that rather similar to our own, more severe, regime? Would you just describe it so that we are familiar with what is happening?

A. The situation in Holland is not exactly as you have described it. Patients, on the whole, will take their prescriptions from their doctors to the pharmacist and the pharmacist will dispense the medicine. The people, on the whole, who are growing for the pharmacists are a firm called Maripharm; they cover about 300 out of 1200 pharmacists in Holland. The other pharmacists, presumably, obtain their materials by a retrograde route back from the coffee shops. Maripharm have developed some materials of known consistency and attestable quality. That supply, between Maripharm and the pharmacists, has no basis in Dutch law; it is, as you say, tolerated, but it is certainly not legal and no licences have been issued. Therefore, we have the odd situation that doctors are allowed to prescribe, patients are allowed to take, the pharmacist is also allowed to store, but nobody has considered where it comes from. That is an unsatisfactory conundrum that I could not imagine would exist for too long in the United Kingdom. The company with whom we have a relationship is purely involved in medicinal cannabis breeding; they do not supply pharmacists or anybody else with materials. So there are two separate issues there. In the United Kingdom, I think, there is no identifiable structure in the same way as the Dutch have—even though it is identifiable it is illegitimate.

694. You say that the Dutch are using clones, which they cannot export because they are plants. I am never quite sure at what point cloning material



28 July 1998]

DR GEOFFREY GUY

[Continued]

Lord Dixon-Smith *contd.*]

ceases to be a plant, but, presumably, single cells of plants would not be regarded as plants. Or would they? Also, is there doubt about the genetic purity of the seed of these cloned plants?

A. There are two questions there. I think, essentially, the safe ground for legislators is that anything that is not a seed is a plant. The question as to "Is a plant really a plant because it is only a small plant?" has not got very far. We have tried that one. The question as to "Well, you are only concerned it is a plant because in its later life it produces psychoactive materials, but whilst it is a very small plant we can analyse it and show that there are no psychoactive materials. Would that not make it a plant?" I think we have not shifted any ground there. Certainly we have had excellent discussions at the Home Office in that regard, and although my licence would allow me to import complete plants the Dutch authorities would not move on that matter. With regard to genetic purity, the minute you grow from a seed you have lost it. You will have most of the genetics and phenotypes represented in the seed line. Hopefully, for breeding you would have a large proportion of the plants that you grow being true to the phenotype.

Lord Butterfield

695. You are saying that seeds have not got any psychoactive material in them, yet, apparently, they can be regarded as sources of marijuana and are, therefore, subject to all kinds of regulations. Is there any point in the development of seeds as small plants, and so on, when legislation says "Now, that is a plant that we have got to control"?

A. I am not sure I understood your question, my Lord.

696. I am just wondering if there is a moment in a plant's development when it passes from being an "innocent" seed to being a "wicked" plant producing this drug?

A. Yes, I think that point can be identified quite closely. Part of our research will be—because I anticipate there will be a change here because the current legislation relates to the science as it was in 1961—that you will not see significant amounts of the psychoactive components until the plant has finished vegetation and begun to go into florescence. That said, I can understand it is quite easy for somebody to say "I know what a seed is, but once you germinate it it is no longer a seed". Can I just say that the seed is not a source of the psychoactive component; there is no psychoactive drug in the seed. What one tends to find is that the seeds may be coated with resin and other materials that dropped on them, but simple washing of the seeds will remove about 95 per cent of that amount. Therefore, our seeds will be prewashed and precleaned.

697. It seems to me a nightmare for legislators, identifying the moment at which something becomes wicked or dangerous or falls under legislation. I have no doubt they will sort it out.

A. I am sure there are those who will invite the legislators to consider the extent of the wickedness.

Lord Porter of Luddenham

698. Dr Guy, you clearly favour the use of the plant-derived drug rather than the synthetic. In fact, in an interview with the *Financial Times* a few weeks ago it was said you believed synthetic cannabinoids can never match the full effects of cannabis, which depend on the combination of chemicals in the plant. I do not quite follow this argument. I do not see the difference between a specified mixture of synthetic chemicals known, and a mixture—hopefully known—which occurs in the plant. You say that the plant products are safer and offer a shorter development time, but does a shorter development time mean that you grow them quickly but manufacture them slowly? Can you explain the reasoning behind your preference for the plant's efforts rather than the chemist's efforts?

A. Yes. Can I, first of all, say that the word "safe" is quite a powerful word in this context. I think I said that these materials are very safe when compared to synthetic drugs. I do think that there may be a case to be made, in due course, and our research perhaps indicates this.

699. Could you just say why would they be safer if it is the same substance—a known chemical?

A. There are three ways of looking at this. I will go straight to my second way, which is philosophy, which I think is probably what we are driving at here. If one accepts that in certain biological processes mediated by drug interventions the outcome of those could be synergised between two materials (one material making another material work 10, 20, 30 or 100 times greater than it would on its own) then the effect obtained from two materials working together is perhaps 100 times each of the materials on their own. To be matched by either of those materials singly would require perhaps 100 times the dose, if there is dosage proportionality. With 100 times the dose, I think we are all aware that as one increases the dose of synthetic material with them are the attendant side-effects. So to obtain 100 times the activity one is risking also obtaining a much larger number of side-effects.

700. I still do not see the difference between those two substances, (A the plant product and (B) pure chemicals, synthesised and then put together in a certain proportion and delivered together in the same proportion as in the plant—unless you do not know what is in the plant. I am assuming that you will know what you are delivering chemically, whether it is in the plant or from a manufacturing process.

A. I think I can understand exactly what you are saying and agree with exactly what you are saying. If man, through his ingenuity and understanding of a myriad of pharmacological, immunological, delivery, elimination and metabolic processes that go together to help a medicine alleviate a group of symptoms or even a complete disease—if we could understand that then we may, at the end of the day, end up with a number of chemicals that are synergising for effect, counteracting for side-effects, optimising for delivery and absorption and optimising for acting on certain receptors and not others. I think man, in his ingenuity, will arrive at that, but we are, in the pharmaceutical sense,



28 July 1998]

DR GEOFFREY GUY

[Continued]

Lord Porter of Luddenham *contd.*]

nowhere near being able to choose the right combination of synthetic chemicals, and we are certainly nowhere near being able to work out the permutations of how those chemicals should be combined, in which way they should be combined, and whether they should all be delivered together. We have seen evidence that when you give one chemical followed by another you get one reaction from a receptor and if you give two chemicals together you get a different reaction. So in the natural plant, the natural plant and man and nature (in this case, not in every case) has contrived over many thousands of years—about 12,000 years—to produce a plant which seems acceptable within the mammalian population, although there is a difference between certain mammals and others in the way they use that product. If it seems to be safe in certain areas and it seems to work, and if it is hypothesised that the way it works is by any more than the synergy of one, two or three chemicals acting together or one, two or three chemicals acting against one another, one would be proposing a pharmaceutical development the magnitude of which the pharmaceutical industry has not seen yet. We simply would not be faced with a choice of: “These synthetic chemicals or this plant”. In due course, I am sure, science—perhaps 50 years out—will be able to say “Whatever this plant makes, in whatever proportion, we will be able to make it synthetically”. At that point that is one way of doing it. Medicine is not sophisticated enough to be able to go and pick half-a-dozen chemicals, mix them and come out with the same answer as nature has done for the last 12,000 years.

701. I think I understand entirely. It is because of our ignorance of the plant constituents.

A. No, it is our ignorance of the medical processes.

702. But if we know the composition of the plant we can synthesise it.

A. Yes, but that is not the problem here. The problem here is if I have in front of me—if I can use an analogy—a perfectly pure example of each of the chemicals in cannabis and was then faced with the challenge of working out which of those in combination will work in multiple sclerosis—perhaps something which requires something more towards the THC end of the cannabinoids—as opposed to epilepsy, which might start at the other end with cannabidiol. If I was given the task of working out the permutations—well, if I was dealing with five materials I have probably got 25 permutations or 25 clinical comparative programmes, 25 toxicology programmes—with each of those synthetic chemicals one would not be allowed or prepared, certainly in our environment, as a pharmaceutical physician, to move forward into man without further toxicology work. Although I understand the scientific purity I do not see the value in taking apart something that appears, at present, to work. I think my role, at present, is to confirm, in a medical setting, that what we have works, and then, very carefully, once we have models that can show us how, try and remove things if we feel it is necessary to do so. Remember, a lot of these chemicals in this plant are there in virtual trace quantities. Some chemicals are there in quantities less than the

unknown impurities that you would measure in a synthetic chemical. The specification of THC, for example, with the FDA is 95 per cent pure, and of that 95 per cent it is allowed to be up to 2 per cent delta-8-THC. So what is the other 5 per cent? It certainly did not come from nature, it came from a distillation column or some sort of laboratory equipment. I would want to know what is in there. I think the important thing is that the materials that we use to move ahead in medicine are of a sufficient quality and consistency to be confident to reconcile current results with previous results and future results.

703. You do not visualise any legal problems from the fact that you do not know what they are?

A. Well, I think a lot of people say “We do not know what they are”. I have worked with a number of plant medicines, a number of which are now commonly on the market throughout Europe. I have to say that the one plant that has received more attention in terms of analytical chemistry and in terms of elucidating what is in it is cannabis, which actually is not an approved medicinal plant. I think we do know what a lot of these constituents are, on the whole, because cannabis is part of the family *cannabaceae*. A simple way of describing it is that cannabis is hops plus cannabinoids. I certainly think that humans have a lot of experience in ingesting hops. My concern over what they are, at this point, is that it is only important to tell me the level of caution and the threshold of caution I should exercise in moving into the most important studies of all, and that is the clinical studies to produce the value of these medicines. There will, no doubt, be parallel research to try and identify single entities with combination entities, and that work, I think, will go on for as long as it probably took digoxin.

Lord Porter of Luddenham: Perhaps I am tending to go round in circles, but I think we are in a bit of a circular argument.

*Lord Butterfield*

704. I suppose you will not be surprised to be asked whether you are descended from the family of Thomas Guy?

A. I went to St Bartholomew's Hospital, my Lord, and no, I am not.

705. My question is concerned with quality control. We have already been talking about the wide variety of chemicals in the plant. We have had evidence suggesting that cannabis grown in different parts of the world may have different mixtures. You, presumably, are going to be concerned with quality control. I wondered whether you could tell us how you are expecting to maintain a standardised plant for investigations? Does it mean a lot of chromatography?

A. Yes, we certainly need a lot of chromatography. That is right. Some of the largest expense is in buying laboratory equipment. If we look at the variety of plants we use, we will be carrying out our research making pharmaceutical grade extracts—and I will not go into that. Looking at the plant we use, because we clone the plant the whole of our crop will be genetically identical. I am not a botanist, but I spend



28 July 1998]

DR GEOFFREY GUY

[Continued]

Lord Butterfield *contd.*]

a lot of time with botanists on this basis, and apart from quantitative yield—the actual amounts—the relative composition of the cannabinoids, terpenes and all the other components of cannabis will be determined by their genetic typing and, indeed, their phenotyping, so much as one genetic example may produce certain chemicals below the equator and different ones above the equator. Within my controlled growing conditions, where we will control the atmospheric conditions—heat and photo-period—by a computer, we should be able, with a genetically identical crop with identical growing conditions, to produce, with the exception of quantity of yield (which may be adjusted up and down according to amount), an identical output from the plants to a standard that can be within international acceptance standards. Some of that work has already been done in Holland producing 97 per cent pure THC.

*Chairman*

706. On what contents will you standardise it? THC will be one. How many of the cannabinoids will you have identified and quantitatively determined?

A. There are three answers to that. First of all, the minimum is the minimum I would require for my product licence. The second one would be those required to carry out research, in my mind, to look at certain ratios of cannabinoids, and the third answer would be as many as we could possibly measure—certainly in the context of this debate. We have instituted already analytical methods for what I believe to be—although using my own model there may be one of the minor cannabinoids that has a major effect—the principal components. We are going to be looking at, initially, THC, CBD, CBC and CBG. We would like to look at the propyl derivative THCV, which is very abundant in Thai cannabis. There has been no work on this at all, but there seems to be a difference in the medical anecdotes coming from those areas. So we will look at those and we will also look at terpenes and other markers of the plant.

707. I am sorry, I think we are at cross-purposes. I am sure you will do all of that, initially, on the plants that you select for breeding from cloned plants.

A. Yes.

708. Having done it, are you then going to rely—in each batch that you make after that—on the fact that you will be dealing with clones, or are you going to measure all these things every time, in every batch?

A. No, indeed not. It is actually a mixture of the two. Normally with a synthetic process one would rely very heavily on the analytical method of the final product. There again, if you have got a product which may have potentially dangerous impurities the method of making, the in-process control is important. What will be very important is control of our starting materials, in whichever process. We will be placing a lot of reliance on the fact that we are starting with genetically identical materials, producing the same ratios of materials—that is genetically imperative. We will be doing in-process quality controls throughout the growing cycle of each plant to make sure that no crop is running off

line, in terms of having been subjected to abnormal conditions. The next question is how do we provide quality control for the final product? That will be a mixture of absolute standardisation of our starting materials—not only the plants but other excipients we use—and the final product, which will contain the plants plus about 20 other chemicals that we have to use as excipients for formulation. It is not necessary in our regulatory dossier to measure every chemical. What we have to do is provide a validated method, which we will validate as a range of constituents and a range of stress conditions, to validate our efforts so that we have a qualitative fingerprint for the product in terms of economics. In terms of accuracy and precision we will want to pick exactly those components which we believe give us a very good indication of the quality of the material. Also, the authorities will ask that some of those components have some relationship to the effects of the product. So some will be related to those effects you will see on humans. Some will be purely quality controlled components; we may pick a marker which we believe is inert and will always be there, and use that as a marker for quality of the content of the material.

*Lord Butterfield*

709. Can I ask you whether it is in your business plan to get products from other parts of the world and to analyse the other ingredients of the different plants? Then, when you come to the question of cloning, is it a board decision which plant you decide to clone, because the ones you do not clone may be available to other people with patents? I would like to know whether you have something in your plans to explore cannabis plants from other parts of the world.

A. Yes. The first thing I have done is secured a relationship with the breeding company in Holland. The members of that company have spent probably the last 25 years scouring the world for every possible medicinal variety of cannabis, and they actually have the world's largest living library in clones—this is the shame, because they are all there in clones—of cannabis varieties, representative not only of varieties coming from different parts of the world but what they have also set about doing is analyse those varieties, brought them back to the northern climates and then re-bred those varieties with other varieties to get those varieties to produce the same profile of content that they do in other parts of the world. A lot of that work has already been done. In terms of choice of moving ahead, that is always a difficult one, but that choice will rest on my shoulders at present; I do not actually have a board at present. Your final question was patents in part of the business plan. We intend to carry out clinical trials to look at the relative components and certain ratios of cannabinoids to see which ones are more favourable in different indications. Once I have a good notion or idea of those, we will start a breeding programme to produce a single plant that produces that ratio and none other. Those will then be registered.

710. It does seem to me that you are very fortunate that those people in Holland have been working on this for such a long time and have provided a library



28 July 1998]

DR GEOFFREY GUY

[Continued]

Lord Butterfield *contd.*]

of plants. Who has been supporting them this quarter of a century?

A. That is a question I asked them, my Lord. I know who has been supporting them for the last six months, and that is myself. They are principally Americans who left America because the environment was not the best environment for doing this research, and went to Holland. They have received gifts, donations and investments from a variety of people, mainly high net worth individuals that are sympathetic to these areas. The names you will find in common with those names that have supported proposition 215. They have been supported in those ways, although it has been long in coming.

*Lord Kirkwood*

711. The chemical nature of the plant that is produced is not just, presumably, a result of the genetics but, presumably, of the environment as well. The environment obviously controls the yield, but does it also control the ratio of cannabinoids?

A. Yes, indeed. The plant, to produce its final output, has to have its genetic coding. Then that forms into other phenotypes and it has to be specific for where in the world it is grown. Remove that plant to somewhere else in the world and it is mainly dominated by temperature and photo-period. If you subject a plant to a different photo-period and different nutrients in the soil (these are the edaphic considerations) you can alter those, but once you have the same genetic plant plus clinically designed growing facilities—our growing facility will look far more like a laboratory than a greenhouse and we have computer control for all aspects of the environment—then consistency is very high.

712. You get that information from the Dutch workers, initially?

A. We have got that information from a number of sources—we, clearly, have it from the Dutch on their legal programmes—but that information is also highly available in a number of other manuals on how to grow marijuana throughout the world. There is a phenomenal amount of literature, and very well-written, in this area.

*Lord Butterfield*

713. How are you going to do your clinical trials? Are you expecting to give the compound you eventually select orally, or are you going to be involved in a smoking product?

A. I think your question was which route and method of administration we anticipate using.

714. Planning on at the moment.

A. I have changed my mind five times in the last six months. Basically, because of my background in drug delivery, I have no shortage of technologies to hand, so access to technology is not a problem—it actually gives me a wider choice. Essentially, most of the evidence that we have for the optimal beneficial effects that we see comes through smoking cannabis. A cannabis cigarette is quite a remarkable little pharmaceutical factory. It provides about 600

degrees' heat at one end and that heat is then used to generate hot air which is then drawn through the materials. Dependent on how moist the materials are, between 6 and 10 per cent, you will get a differential distillation of the active compounds of the different chemicals within. That then recondenses further down the cigarette and then are re-volatilised as they get warmer again. So what we have is something that is heating materials, which provides for decarboxylation and, therefore, activation of the material. It is said that the cannabinoid acids are not active—although it is now being said that perhaps they are—but let us work on the premise that they are not active until they are at least heated. Under that circumstance I think we can probably consider that the materials that come out of that cigarette will come out not altogether, they will come out like a column. That type of delivery is very special indeed. Then we have the advantage, from that, of rapid absorption into the lung and, also, the oropharyngeal mucosa. If you look at the droplet size that comes out of these smoked routes, especially for people who use bongs then they are getting much higher droplet sizes. So it is rapid absorption of material which is, essentially, not metabolised by the liver, and that is very quick. The great advantage is that the patient can very quickly titrate the dose they require, and we hear from most patients that they are able to obtain a dose which will relieve their symptoms, especially in multiple sclerosis, yet not take them to a level where they obtain the unwanted psychoactive effects. I would suggest, in the medical context, that the psychoactive effects are, in effect, overdosage of this medicine. So that route, the smoked route, is a very, very intriguing route indeed, and it allows patients to auto-titrate. I have had reliable reports that some patients with extremely severe multiple sclerosis, with pain and spasm, find that their pain and spasm obtunds—it goes away entirely—within 45 to 55 seconds. I did not believe that until I sat down with Dr Paul Consroe, an American whose name I am sure you are familiar with, and he said "Yes, I see the same". I have spoken to other clinicians who have said "Yes, sometimes one or two minutes but sometimes that quick". When you consider that, the actual dose of the drug—whichever one it is (and it may be cannabinodiol getting there first and THC 20 seconds later and is having differential effects)—is an extremely small dose. This gives me the mind to believe that the psychoactive doses will be shown to be way out of the top of the therapeutic range, especially when we apply good, sensible drug delivery. So the smoking route is enticing. What I intend to do—and we have a patent running—is to reproduce that in a special gadget which is a mixture between an aerosol and a vaporiser. I am sure we have all given medicines to our children by putting a candle under some plant extract floating in water (a Wright's vaporiser). So in a modern device we will be providing an activated, vaporised, non-particulate extract of cannabis. In the oral sense, however, I have recently begun to hear of indications where the patients specifically say they get better relief from taking the medicine orally—not in MS but in other conditions. I would like to look into this further. They get better relief orally, plus, of course, the effects last longer. So although it takes an



28 July 1998]

DR GEOFFREY GUY

[Continued]

Lord Butterfield *contd.*]

hour to take its effect you get 7 or 8 hours' relief. This is commonly understood. So the patient who has acute pain and wants acute relief is not going to want something that is going to start taking the pain away an hour later. Somebody who has a chronic condition who wants relief from those chronic problems will, perhaps, be very satisfied with a well-titrated dose orally. So those are the two things, and I have not decided, at present, my Lord. In fact, I will use the initial pharmacokinetic and pharmacodynamic studies in different patient groups to guide me as to the best candidate, whether it is suppositories, skin patches, nasal inhalers or dry powder.

715. I have already raised with someone else the possibility of using the ill-fated artificial cigarette product. I do not know whether you have considered putting your extracts into plastic wood and smoking that. I gather that it is very common for people to put marijuana in with tobacco and make a cigarette, or a joint. Have you talked to the tobacco people about the ill-fated "safe cigarette" as a possible vehicle for smoking?

A. I do not believe there is a safe cigarette, so, no, I have not at all. In many years of drug delivery we have never had cause to speak to the tobacco people, with the exception of Japan Tobacco, which owns a number of pharmaceutical companies. I think it is a possibility, certainly, but I think that one would have to chemically activate the materials within that source to be drawn into the lung. Certainly a modification, like the newer nicotine devices, may well fit, but of course it will have the advantage that the patient will be able to moderate their intake for rapid effect, and then titrate a further intake. It is a route that forms part of the chosen route, but I do not think I would be dealing with tobacco companies, in the short-term.

*Lord Soulsby of Swaffham Prior*

716. Did you mention the suppository route when you were talking about the route of application?

A. I just did, a few moments ago, my Lord. The suppository route, of course, is an interesting route and has a lot of merit. About two-thirds of the suppository should be absorbed into the systemic circulation and bypasses the liver, provided you get to the upper two inferior rectal veins.

717. The other thing that flows from different methods of application is: will you be monitoring the levels of cannabinoids in the bloodstream in the patient to determine the relationship between levels and relief of symptoms?

A. Yes, indeed. Monitoring concentration over time and monitoring blood level over time is absolutely stock-in-trade in drug delivery. I will be monitoring, in the first instance, to see that I am getting it in consistently with the devices used, and as we then elevate doses from low doses to high doses we will, at the same time, be looking at the pharmacodynamics—the effects it has on the patient. There is a suggestion in the literature, and it would not surprise me at all, I have seen it in natural products before, that at very, very low doses, if they can be delivered consistently, one may get one set of

physiological-type outcomes and, at the higher doses, nearer the ones we use at the moment, what I would consider to be supra-physiological outcomes.

718. Is the very rapid effect that you describe for inhalation associated with a high level of cannabinoid in the circulating bloodstream?

A. That is what I would be curious to look at, because the peak effects occur at about ten minutes and after, perhaps, the third, fourth or fifth puff of a cannabis cigarette from the data that has been put forward. We see a marked clinical effect, really, at the very first arrival of the very first amount of drug getting to the brain. One does not see that very often in medicine. It also provides me with an excellent model, of course, to test my delivery to those sorts of patients. I think that first effect may be occurring at much lower doses—although this is speculation—than will eventually occur 10 or 20 minutes later after the intake of cannabis.

719. Do you have plans to collaborate with other organisations, such as the MRC and the Multiple Sclerosis Society in your proposed work?

A. There are two answers to that. From here to product licence approval there is only one authority which should be arbiter of our research, and that is the Medicines Control Agency. So it is quite possible to do all this work without any such collaboration. I think, in this instance, it is extremely desirable that as many of the interested parties do collaborate. We have an area of science that has been littered with mis-information and myth. We have already spoken with a lot of the people interested in this area—although not with the Medical Research Council, I must say. My licences, I feel, could act in two ways: one as a magnet and the other as a pebble with ripples going outwards. Either way, I think there will be an increase in noise in terms of more scientific activity. I would be delighted to work with the societies, especially as some of those societies are very good sources of funding.

*Chairman*

720. How long do you think it is going to take to persuade the authorities to give you a licence?

A. There are a lot of ifs and buts, of course, moving from here to a licence. I think the easy way to answer that is that I do not believe a licence will be issued before the end of four years, and certainly probably not before the end of five years. Once we get to five years, then we will be in the target zone in terms of time, dependent on the extent and quality of data we have gathered at that time, on the basis of quality, safety and efficacy. If we have a good dossier, a confident dossier, by the end of four to four and a half years; so then I think five years may be a reasonable time frame to expect the first licence. Pharmaceutical development is dogged with delays, so I would say about five years for the first opportunity.



28 July 1998]

DR GEOFFREY GUY

[Continued]

*Lord Kirkwood*

721. If your clinical trials are successful, then G W Pharmaceuticals will not be able to market a cannabis derived product for general medical use unless it is removed from Schedule I of the Misuse of Drugs Regulations. How difficult do you think it is to get to that stage; to overcome that hurdle? Could you give us a time estimate on that as well?

A. First of all, that hurdle could take two forms. If the product that is approved by the MCA is an extract of cannabis, then that hurdle will be something between the Government and consent of Parliament to reschedule from Schedule I to Schedule II; with subsequent notification, I believe, to the INCB, the International Narcotics Control Board, and that is under the Narcotics Convention 1961. If a product is a single cannabinoid then it comes under the Psychotics Convention 1971. Therefore, in between the product approval and Government suggesting to Parliament that it should give its consent, the World Health Organisation will have to give its approval. So my own cannabis route is also a route which is more domestically orientated in terms of relying on our politicians. Therefore, your question really comes down to: to what extent can I rely on what I have been told by the politicians? The Government has said in the House of Lords in replies to questions, and in the House of Commons and in debate in the House of Commons, and also in written replies from the Minister to various people, that if a product is approved by the MCA, the initial response to that is that they would move the product from Schedule I to Schedule II. As I pointed out, it would require the consent of Parliament. If one has a massive majority then it would be achieved. So I am relying at present and putting a great amount of trust on what we have been told by the Government. I actually think that if the Medicines Control Agency says this is a medicine, then the product technically should not be in Schedule I in any case. Schedule I is for those materials of no therapeutic value. So the main debate is what Schedule it should go into. I trust in our Government and their officials.

722. So, let us say, starting from what you are doing now, you might put in another couple of years before you get to the point of clinically proven trials. Are we talking in terms of about three to five years?

A. Past the next election would certainly be the right answer. The pragmatic phase of the research on our first candidate—because this research will not take the form of a single product going forward in single indications—we will start the process of approvals, I hope, sometime in five years' time; and we will probably carry on for another 25 years, we hope.

723. The first stage.

A. The first pragmatic stage, I would probably know in my mind and my scientists will know that we have a product, which is eventually going to be approved, probably within about two and a half years from now. To the data that I have at that time, I will have to add in greater numbers of patients, longer exposure for greater safety, look at sub-groups of respondents, those sorts of things. So the pragmatic phase will be about two and a half years. There will be a further descriptive phase of about another one and a half years.

724. So it will be about five years?

A. Four years to application. Another year of deliberation.

*Lord Porter of Luddenham*

725. Do you have any funding problems for G W Pharmaceuticals over this fairly long period?

A. Having spent 13 years raising about \$70m for pharmaceutical research, funding is a challenge, my Lord. It is a problem if you cannot find any. So far, this whole programme has been funded by myself, and the quicker we do find the appropriate sort of funding the quicker all these avenues of research will be able to be elucidated.

726. What sources would you hope for apart from your own pocket?

A. The most likely sources will be those sources which have already sponsored the medical use of cannabis. I imagine we would be talking about high net worth individuals who have expressed, either publicly or privately, their support for medicinal cannabis programmes. Certainly this is where the first interest lies. There are too many variables at present to encourage the classical venture capital routes, perhaps. I think also that the new research here, which is very much patient demand led, will be accompanied by funding for research programmes—not particularly for our in-house activities—from the representative bodies. The MS Society has already said they would support clinical trials for MS patients. I am sure a lot of patient groups will have equivalent societies or bodies to help them. As yet, I see no prospect of any funding from Government or central resources.

727. From pharmaceutical companies?

A. Pharmaceutical companies certainly. If we look to about two and a half years' time, where I have reasonable proof of concept, if I step back about 12 months, then, I'll have a dossier which will show a pharmaceutical with enough clinical activity to license out the products—I have personally entered into about a hundred licence agreements over the last 13 years. I am absolutely confident that once we get to that two or two and a half year stage, that the pharmaceutical industry will step back in again to be able to take over these programmes from us. But they have not been very interested in doing what we have done to date; getting involved in all of this.

*Lord Kirkwood*

728. You do not see the tobacco companies putting money into this?

A. I do not see it being accepted.

*Chairman*

729. We have pursued the quality control side of this but we have not pursued the question of efficacy very much. What would you be starting off with in your first research programmes with human volunteers?

A. I think I would probably not want to use too many volunteers in the first instance. Generally, when one carries out volunteer studies in this country you are talking about subjects who are younger,



28 July 1998]

DR GEOFFREY GUY

[Continued]

Chairman *contd.*]

maybe students. We could of course define the age group. But I think there would be a ready population of patients under the control of the numbers of physicians who are experienced in these early studies. With our presumption of safety, I would be confident to be able to start by studying very small groups of patients, to look at tolerability of a single dose and then move on to multiple dose, by which time we may want to add in some additional laboratory work. What I am looking for is to be able to get to the right doses; to dose-range my studies in a suitable clinical model. Now MS represents a very good clinical model because we have patients saying that they take the medicine and a few minutes later the symptoms improve. That is really a joy of joy to a pharmaceutical developer, to have such a definitive model very early on in the programme. So we would be looking at those sorts of patients, perhaps also a bladder spasm and incontinence model. We have already had certain discussions in that area in Queens Square. To be able to look at a number of things. That would really be testing the acceptability of the materials, the acceptability of the dosage form, looking at pharmacokinetics and pharmacodynamics in parallel. Beginning to dose-range; an upper dose range scale; starting from very, very low doses to see if we have missed a lower end of dose range. Also, evaluating exactly at what point we might start to begin to meet some of these other unwanted effects of over-dosage. So we would want to do that in perhaps patient volunteers as opposed to healthy voluntary volunteers, if you understand my meaning, human volunteers without any disease process at all.

730. To persuade the Medical Control Agency that cannabis has any therapeutic value requires a fair amount of work. On MS, there is a very large amount of anecdotal evidence.

A. I think certainly MS seems to be at present, with what we know about it, a very, very promising indication in terms of being able to demonstrate the value. Once we have one model, in which we have clinical evidence demonstrated of a safe and consistent product, this whole issue might go back to being a pharmaceutical development rather than something which is attracting a lot of attention as at present.

*Lord Porter of Luddenham*

731. Is there not also another requirement really, that there is no existing treatment which is as good or better?

A. The requirement would be what, my Lord?

732. Justifying the use of cannabis for MS treatment or anything else would be difficult if there are already drugs which are as good or better.

A. No, I do not believe so, certainly in the United Kingdom. If we went to Norway that would be the case. They put in an economic evaluation and also a comparative evaluation of a drug. One applies for approval here on the base of quality, safety and efficacy. If one can demonstrate that this material is of an appropriate quality, appropriate safety, for the indication for which you are treating, so it shows that it is efficacious, the authority would be mindful to

approve. It would certainly be a marketing advantage if no doubt we could also show at the same time that it is superior. If you have a product that works where no other western medicine works, then the confidence with which you can move forward and the ease of demonstrating that product's ability to work is much greater. Therefore, your studies can be smaller. If we have measures which are more sensitive and more specific your development time may come forward again.

*Lord Nathan*

733. How big an obstacle do you feel the present legal and regulatory framework is to research in the cannabis area? I particularly noticed your comment in paragraph 1 of your note which says: "The MCA has been able to provide invaluable advice on specific aspects of the regulatory requirements for standardised whole plant extracts."

A. Yes. Obstacles seem higher when you are about to get over them and a little less when you have been over them. One of the major obstacles we have already passed. Therefore, I would view it in a different way from someone who was trying to approach those obstacles. In our long discussions and dialogue with the MCA over many years about the ways in which to approach the approval of plant-based medicines—a medicine that will require a full product licence, which would not be going through the herbal medicine route, and falls somewhere between a botanical and a phyto medicine—the MCA have been very clear in their advice and guidance as to what should be achieved. One of the bell-wethers of what they have said is control of starting materials. I believe that we designed this programme not to go out into the fields and pick wild cannabis. This is a scientific programme where we know what happens to this plant. Each of our plants will be numbered. When one takes a final dosage form we will know from which plant or plants that was made. That has been an agreement between myself and the Home Office. It seems eminently sensible because we are liable to change things. So with regard to the MCA, what we can do is to put together evidence on quality, safety and efficacy. Discuss with them very regularly, as they invite us to do, and to ensure that the most difficult area, which is the control of starting materials, is taken care of. The next hurdle is whether Government or officials will be true to their current word. I fully believe and trust in them that they will be. So the other area is: does the correct legal framework cause a problem for this research to go ahead? There is no doubt that if there was a different framework there would be an enormous amount of research going ahead. One rarely sees such a massive scientific and medical literature for a pharmaceutical which does not actually exist, in terms of cannabis, so the research would go ahead. Possibly in an unco-ordinated way: at present moving from something that a few years ago would not have had popular support, either medical popular support or even of the country; in a move from that situation to this situation, the current framework has served its purpose at present. It is not easy. It has not been easy at all. The safeguards we

28 July 1998]

DR GEOFFREY GUY

[Continued

Lord Nathan *contd.*]

have had to put in place to be able to develop these medicines are really probably some of the most extreme but not more so than developing cytotoxic medicines, not more so than developing steroids, for example, where health and safety of your staff is of the utmost importance. So all of the measures we are taking fall within the normal but somewhat extreme parameters of work in the pharmaceutical industry. We have been used to working with morphine for a long time. But certainly the current legislation will discourage an awful lot of people from moving into this research. The people that do will have to cover a wide area of expertise to be able to do it.

*Lord Butterfield*

734. Do you envisage that there may be a problem with the number of trials which are suddenly flooding in, which may be using all kinds of products which may or may not be very well recognised scientifically? Your plants are going to be numbered but surely some of the people who may step forward, if it looks as if there is going to be clinical research in this field, may have quite different qualities of material. This could cloud the issue very seriously.

A. At present, I do not believe there would be an issue there, in as much as each researcher who would want to do work with cannabis, the clinical researcher will have to have a licence for the purposes of medical research. That licence will have to specify the source of supply: at present or very soon a recognised and analysed source of supply; and in due

course batch documentation, release documentation. Doctors will need to be cautious to undertake research with street material of unknown quality, which quite often has other materials mixed in with it. A lot of the history of cannabis and the myths about cannabis came from some of the early reports where the early doctors, in fact, were reporting on the effects of opium which was mixed in with cannabis, Indian opium. So it would be of less—I would not say little—scientific value to undertake clinical research on unstandardised material, or material which could be dangerous.

735. Of course.

A. The current legislation will prevent that.

736. The registration of the people, who are going to do the research, will be an important early step in the developments that are to follow, presumably?

A. Within our programmes I am responsible under licences to control all those aspects of supply and materials that are used, not only so that the results that we get are valid but also for these legal reasons.

*Chairman*

737. Is there anything that you think we should have asked you that you would like to add?

A. I do not think so, my Lord. The questioning has been quite exhaustive.

738. In that case we are extremely grateful.

A. Thank you.



WEDNESDAY 30 SEPTEMBER 1998

## Present:

Butterfield, L.  
Butterworth, L.  
Dixon-Smith, L.  
Kirkwood, L.  
Nathan, L.

Perry of Walton, L.  
(Chairman)  
Porter of Luddenham, L.  
Soulsby of Swaffham Prior, L.

## Examination of Witness

PROFESSOR WAYNE HALL, Executive Director, National Drug and Alcohol Research Centre, Sydney, Australia, was examined.

*Chairman*

739. Professor Hall, thank you very much indeed for coming and for sparing this time out of a very short stay in London, we are most grateful. We, of course, have read your written submissions with great interest and have paid a lot of attention to them. Could you say something about yourself and tell us about your most recent work in the area of cannabis?

(*Professor Hall*) Yes. I am a director of the National Drug and Alcohol Research Centre in Sydney, which is a centre funded by the Commonwealth Government of Australia to undertake research on drug use, drug related harm and the treatment of drug dependence. I have been in that position for ten years. My interest in cannabis began when I was commissioned to review the health effects of the drug for the Australian Government, and I think that is a report which you have seen; on the health and psychological effects. Since undertaking that review we have become quite interested in the topic of cannabis and have undertaken quite a bit of work on cannabis dependence, the characteristics of long-term users. We are about to finish a trial of psychological methods of helping people to stop who have become dependent on cannabis. I think that is the major work we have been doing on that. We have also just recently produced an estimate of the prevalence of cannabis dependence in the Australian population as part of our national survey of mental health.

740. Have you anything you would like to add to your report at this point?

A. Not to add. I would be quite happy to answer your questions or elaborate on any issues which I mention in there.

741. Can I ask you what the latest thinking is on the unconfirmed but possible adverse effects of cannabis which you noted in section 1 of your paper, especially bronchitis and cancer, residual cognitive effects, and risks to the unborn child?

A. I will just go through those quickly. I think there is no doubt about the impact of cannabis on bronchitis. I think the high prevalence of symptoms of bronchitis in chronic cannabis smokers has been sufficiently observed, and we have seen it in our

studies as well, that we can be confident of that connection. The cancers are less certain, and I think that is going to be very difficult to resolve. The technical problems involved in doing a research study which would enable us to answer that question are fairly substantial, although I think it still remains a research priority. In terms of competition for scarce research funds for other forms of cancer it is probably well down the list, largely because the number of people who are engaged in the pattern of heavy cannabis use which puts them at risk of developing those cancers is fairly small. I still think it is a reasonable bet that it does cause those forms of cancer. Residual cognitive effects—I do not think that has changed. Again, I think we can be confident that chronic heavy cannabis use produces detectable changes in cognitive function. They are reasonably subtle and difficult to detect, they require sophisticated methods of investigation, but I think it has been sufficiently demonstrated by a number of investigators repeatedly that they are there. I think the argument now really has to be about the significance, how serious are those impairments, can they be reversed if people abstain from using cannabis. Those are the questions which remain to be answered. The impact on the unborn child still remains uncertain. I think the low birth weight effects are the most probable adverse impact of use. Again, I think it is going to be difficult to improve on that situation because the number of women who use cannabis during pregnancy is relatively small and many of those who do smoke the drug also use alcohol and tobacco, which makes it difficult to disentangle the contribution cannabis might make from those other drugs.

742. Anything about the immune system?

A. There is a review. I am not sure if the Committee has received copies of documents prepared for the World Health Organisation review but there is a very good review of the literature on immunity by Dr Klein in that. It is largely based on animal evidence which indicates certainly that the immune system has some variety of cannabinoid receptor present and cannabis does act on the immune system in animals in higher doses. The issue remains the uncertainty of extrapolating those findings from animal to humans under normal

30 September 1998]

PROFESSOR WAYNE HALL

[Continued]

Chairman *contd.*]

conditions of use, but it obviously remains an issue and it would be an issue in terms of potential therapeutic use of cannabinoids in people who might have impaired immunity as a result of conditions like AIDS or as a result of medical treatment with cancer chemotherapy for example.

743. They do not yet know what the cannabis receptor is doing?

A. No. As I understand it—and it is not an area I want to claim any expertise in, it is a very technical field and I am only reporting on what I understand from Dr Klein's review—as he put it, there is a cannabinoid receptor which appears to be different from the one which is present in the central nervous system on which cannabis operates to produce the psychoactive effects.

*Lord Soulsby of Swaffham Prior*

744. It is clear you regard cannabis as a dependence-inducing drug and I think, first of all, we would like a definition of dependence

A. Certainly. A large part of what people have understood conventionally by dependence or addiction has been driven by our experience with alcohol and opiates, and that is to assume that the drug is only addictive if it produces a severe withdrawal syndrome on abstinence. Part of the reason why people have been sceptical about cannabis dependence has been the apparent absence of that sort of syndrome. I say "apparent" because it has not been widely reported, but I think the evidence is reasonably clear from laboratory studies and from more recent human studies, including our own, that with very heavy cannabis use people can experience withdrawal symptoms when they stop using. They are not as marked as those for opiates or alcohol but people do have difficulty stopping because of those withdrawal symptoms. I think the more important reason for believing that it is a dependence-inducing drug is less to do with experiencing withdrawal effects on abstinence than the fact that people become pre-occupied with the use of the drug, their lives revolve around procuring, using, recovering from the drug, they find it difficult to control their use of it, they persist in using it when they know it is causing them harm or exacerbating conditions and they find it very difficult to stop. In these senses of dependence, I do not think there is any doubt that some long-term users become dependent on the drug.

745. Would you comment on the concept that to some extent it depends on the amount of cannabis used, because we have heard from other witnesses that the amount of medical cannabis used to control pain and all the effects of Multiple Sclerosis, for example, is at a much lower level that will not lead to dependency when you stop using it?

A. Yes, I think that is an important point. I would not want to leave you with the impression that cannabis has a high risk of producing dependence on any single occasion of use. The people who we studied who reported symptoms of dependence in the sense I indicated are people that typically use it every day in large quantities, day in, day out; week in, week out for years, very often. The average person seeking assistance to stop cannabis in our trials is someone in

their thirties who would have initiated their cannabis use in their mid- to late-teens, so they have had 15 to 20 years of daily use. That is an order of magnitude different from, as I understand, the most likely therapeutic use of this drug, which might be for acute implications for limited time periods. I suppose the situation where it might become more of an issue is where the cannabinoids might be used chronically to deal with some underlying condition, perhaps in the case of chronic pain or perhaps in managing some of the symptoms of Multiple Sclerosis or other neurological conditions. I think that for a lot of the potential therapeutic uses of cannabinoid drugs, dependence and tolerance would be of minimal concern. In those cases where it might be of concern—with the chronic long-term use—the issue might well be that that is a cost, as it were, that is incurred to obtain relief of symptoms.

746. Can I turn what you said round a little and pose the question: would you say that in the majority of medicinal uses of cannabis the danger of dependence is small?

A. I would think that would be a reasonable statement for a lot of the potential uses. I am thinking, for example—just to name some of them—of its use in dealing with nausea and vomiting in cancer treatment. That might be something that occurs over weeks and months and would be a fairly episodic condition. The risk there would be a lot less than a comparable use of opiates for post-operative pain.

*Lord Porter of Luddenham*

747. Still on the matter of dependence, you say that as many as 80 per cent of those who meet the criteria for dependence do not seek treatment.

A. Yes.

748. Does this mean that cannabis dependence does not worry them; that it is a problem that some of them can live with—like dependence on other things, like coffee?

A. Yes, I think there is a variety of reasons. I think there are a couple of points to make there. One is that that is not peculiar to cannabis. If we look at population surveys on alcohol dependence, nicotine dependence and even opiate dependence in the community, it is usually only a minority of people who meet the diagnostic criteria who seek treatment. I do not think cannabis is peculiar in that sense. I would suspect that probably fewer people who are cannabis dependent would seek treatment for a number of reasons. One is that there are fewer serious medical complications in chronic cannabis users than there would be with an equivalent abusers of alcohol. You do not see the serious gastro-intestinal and other complications of heavy alcohol use in cannabis users, for example. So there are fewer immediate symptoms. Certainly in people who seek help for cannabis dependence the most frequent physical symptom is chronic bronchitis. In terms of physical complications that drive people to treatment, then there are fewer of them. It is also true with cannabis, as with tobacco, that a lot of people who are dependent do succeed in stopping; they persist in trying to stop and eventually succeed. We know that



30 September 1998]

PROFESSOR WAYNE HALL

[Continued]

Lord Porter of Luddenham *contd.*]

happens with alcohol and tobacco as well. There are two reasons why people are less likely to seek treatment. One is that a lot of the existing services are unattractive to people who are cannabis dependent; they do not see themselves as being like alcoholics or addicts, for example. Also, a lot of them are reluctant to present because everybody tells them there is no such thing as cannabis dependence. We have found that if you make people aware of the existence of the service and you offer help, then you really have no difficulty in attracting them. That is what we have found—as have people in the United States.

749. What percentage, or proportion, of this 80 per cent, would you say, avoid treatment because of embarrassment about it becoming known?

A. It is a bit hard to know. We may well be attracting a particular group, but the people we see are often middle-class people with families and jobs and they are, largely, unremarkable; it is a guilty secret that the cannabis use which initiated in their late-teens has persisted into their early thirties. I think the more frequent history of cannabis use has been, typically, that if they get involved in patterns of heavy use it is usually in their mid- to late-twenties that people tend to stop, and the reasons they stop are the reasons a lot of people reduce their alcohol intake—they get married, have children and assume responsibilities. That has an immediate effect on their drug use.

*Chairman*

750. What is the prevalence of dependence in Australia?

A. In the adult population it is about 1.6 per cent. That was for everyone over the age of 18. I cannot give the exact figures for the younger age groups, but it is obviously much higher in the 18 to 35 age group. Our figures are reasonably comparable to American figures. I should say that our figure refers to the last year. I can organise to forward or send a copy of the relevant report which has that detail in it.

751. In Part 4 of your submission you sketch the evidence in favour of medical use of cannabis, which you characterise as largely suggestive and anecdotal. This is the attitude of the BMA, the attitude of the Government and it is the attitude of the Medicines Control Agency. The law is very complex, because to use it medically it requires that it ceases to be illegal, which means it has to be moved from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations. Also, to use it protected, as a doctor, requires a licence from the Medicines Control Agency. Do you think that the anecdotal evidence is sufficiently strong to justify allowing doctors to prescribe it unlicensed? That, of course, is a relatively simple move, compared to getting a licence. Getting a licence, I think we would all agree, requires a clinical trial and strong scientific evidence, but the use of the unlicensed material by a doctor who wishes to use it is a different matter. What is your opinion?

A. I think that raises larger issues about the regulation of pharmaceuticals and medicines. If we are applying the same standards to cannabis as to other drugs then I do not think there is a case for doing that. As people have often argued that our

regulations are too rigid and strict for a variety of remedies, if you are going to make a general case on these grounds there might be a reason for including cannabis in that. I think it very much depends on that larger issue. There is also the argument that Bakalar and Grinspoon put (on the grounds, I suppose, of civil liberties and individual freedom) that we should have the right to use the drug for medicinal purposes. If you apply the usual rules I think it would be hard to make a special case for cannabis without creating a similar precedent for a variety of other substances that people might want to use for cancer treatment or AIDS or a number of other conditions. I think we have had similar arguments put up in Australia and the US for things like Laetrile and recently—a cancer treatment in Italy. It is something that recurrently arises. We have had it in the treatment of opiate dependence with alleged miracle cures from Israel that people have said we should be implementing in the absence of evidence. I am always a bit nervous about creating special cases because of the precedents that arise as a result.

752. You are not moved by the fact that cannabis has been used for over two millennia?

A. I think there could be any number of other things that one could make similar claims for. I think it is a matter of trying to be reasonably consistent on the application of rules across substances. In the case of cannabis one might argue that used in small doses for medicinal purposes it might well be benign and, at worse, probably useless, but I think the concern would be that allowing that special case would create a precedent which would allow others which might be more dangerous. I think that would be the argument against it.

*Lord Butterfield*

753. You suggest in evidence that tetrahydrocannabinol may be useful against glaucoma and asthma. We have been told in glaucoma the effect is too short-lived to be clinically useful and that for asthma better drugs are available. Do you nonetheless have evidence that these indications should not be ruled out in our considerations of the possible use of THC?

A. I would indicate very clearly this is an area I would not claim to be an expert in. Certainly my understanding of the evidence of others who are much more expert than I is very much consistent with the views you have just put. In the case of glaucoma, THC does have effects on intraocular pressure which are of the desired sort, but it has not proved to be therapeutically useful because a tolerance develops to those effects fairly rapidly and it is not an agent suitable for topical administration, which is largely why it has not been used. As I understand it, in order to achieve a therapeutic effect people have to absorb it systemically and they have to experience the psychoactive effects. In the case of asthma, Professor Tashkin who has done quite a bit of work on that and has said there was certainly promise in the immediate impact of THC on the respiratory system, but I think it has proved again very difficult to find a delivery system which was suitable and which produced a therapeutic effect without other undesirable effects.



30 September 1998]

PROFESSOR WAYNE HALL

[Continued]

Lord Butterfield *contd.*]

The question is really one for basic scientists and the pharmaceutical industry as to whether it is worth pursuing or not, and I would not have an opinion on that.

754. And they will need resources too, presumably?

A. Yes. It is not only scientific, it is a commercial issue in terms of whether it is worth investing resources in it.

Chairman

755. In this country we have got a lot of interest, and there is in the United States even more, in cannabinoid pharmacology, and significant clinical trials of cannabis itself are being prepared by both academic and industrial groups. Is there a similar level of interest in Australia?

A. There is. There has certainly been public agitation for some trials of cannabinoids rather than cannabis, usually THC, the pure form. The indication that has aroused most interest is its use in AIDS to stimulate appetite and reduce nausea. There is a proposal under discussion and has been for sometime to undertake a trial of cannabinoids in that particular condition. I am not exactly sure where it is up to at the moment but there certainly has been discussion on doing that. I think I should say that there is not a large pharmaceutical industry in Australia or a lot of expertise in the cannabinoid area, so that has been a bit of a hindrance. We will be looking with great interest at what I understand clinical from the media are proposals in Britain to undertake trials for some of these indications.

Lord Nathan

756. Professor, are there any parts of Australia where use of cannabis for either medical or recreational purposes is to any extent permitted?

A. It turns on that phrase "permitted", I think probably "tolerated" might be a more accurate description. In some Australian states, most notably South Australia, the Australian Capital Territory and the Northern Territory, it is still technically a criminal offence to possess and use cannabis. However, if people are detected in that activity and they possess less than certain statutory amounts then the maximum penalty will be a fine. If they pay that fine, no criminal conviction recorded, and they are not at any risk of a prison sentence. In the remaining states, the penalties still nominally, including custodial penalties, but in fact the courts are very reluctant to do anything other than levy fines. Very recently, two states, Victoria and Western Australia, adopted something like the British system of cautioning first offenders. So for recreational purposes, there is a sort of tolerance, I suppose; either *de jure* in some states or in most cases *de facto* tolerance of recreational cannabis use. In the case of therapeutic use, I am not aware of any statutory changes that would permit it although there is plenty of anecdotal evidence that it occurs. There have been some well publicised cases where people have acknowledged in the media that they are using cannabis for medical purposes. I am unaware of any

cases which have appeared before the courts. I suspect that the police would be very reluctant to bring charges and judges and juries would be reluctant to convict in these cases. So, again, in the therapeutic area we have got *de facto* tolerance even if it is not officially permitted.

757. We had some evidence from Holland that in effect the position with regard to those who consumed cannabis was very similar to the sort of description you gave, but that the commercial exploitation of cannabis and making a great deal of money out of it is stamped on there. I wonder if that is the sort of distinction which you think would apply in Australia?

A. Yes. The police are very vigorous in prosecuting people who grow and distribute cannabis. I think that can have unintended consequences, and one of the most notable has been the police have been particularly effective in closing down large scale cannabis plantations—using satellite, over-flights and helicopters—which has created an incentive for indoor cultivation of high THC hybrids. I think that is one of the unintended consequences, perhaps, of the success in that particular form of law enforcement.

Lord Dixon-Smith

758. We had a paradox revealed to us in Holland under which it was "tolerated"—though not legal—for cannabis to be sold through these coffee houses, but it was illegal for them to purchase the substance. There is a real difficulty here, because there is a move towards greater tolerance than there used to be for the use of cannabis, but if you are going to tolerate its use yet stamp on its production and distribution, you have the seeds of a logical problem there which is going to take some resolving.

A. Yes. I think that is a fair observation. The American sociologist, Robin Room, who has done a lot of work on alcohol prohibition, has described the situation we are talking about with cannabis as an unstable option, inherently unstable. In fact it reproduces the situation which prevailed under alcohol prohibition in the USA where it was not an offence to use alcohol, but it was an offence to manufacture and sell it. It is a very difficult legal situation, a type of institutionalised hypocrisy. As the Dutch often say, it is legal to sell it at the front door but not legal to purchase it at the back door to produce the supply. In the long-term I think that is the situation that people do have to resolve. It is a societal compromise that is necessitated by the widespread use of the drug by young adults and the reluctance of the community to prosecute the law to its full extent in these cases. I do not know what the resolution should be but I think the most likely outcome in the very long run is that cannabis will end up as a product that is available in some way like alcohol, tobacco or coffee. I think in the very long run (I do not expect to see it in my lifetime) that might be the sort of thing that ultimately arises, if current policies and trends continue.



30 September 1998]

PROFESSOR WAYNE HALL

[Continued

*Lord Porter of Luddenham*

759. Would you not agree that the real offenders are the producers rather than the consumers? I am not talking generally, I am talking about the producers of drugs and harmful things like that, because it is only a short step from becoming a pusher. Surely that is harmful.

A. Yes.

Lord Porter of Luddenham: It is encouraging use by young people and so forth. Whereas the consumer is harming only himself, the pusher is harming thousands of people.

Lord Dixon-Smith: I am afraid, my Lord Chairman, I take a fundamentally different view on that particular question. If there was not demand from the consumer nobody would bother to produce at all. So the beginning and the end of the problem is the consumer, not the producer. I accept all the problems of marketing and everything else.

*Chairman*

760. If Parliament in any one country legislates to make the use or any handling of a substance illegal, then the consumer is as much at fault as the producer. It is an anomaly; it can only bring the legislation into disrepute if tolerance is practised officially by the courts. So the only other way to resolve the problem is to allow the use of the material legally. That brings us back to what I was saying earlier, that the use of the material for medical purposes is different from other uses—for recreational purposes.

A. Would you like a comment on that?

761. Yes.

A. I think certainly the two uses are distinct. I do not think there is any doubt about that. I think it would be possible to regulate cannabinoids for therapeutic use in a way that distinguishes them very clearly from recreational use. I think the difficulty would be if one were to make it available medically in the way which I understand and which I think you are suggesting, which would be to allow doctors to prescribe it. I think we would end up with the situation we see in the United States at the moment, particularly California, with the blurring of the boundaries between therapeutic use and recreational use, with some people taking the view that all use is therapeutic, and we would end up with potential corruption. An unknown but interesting sideline of alcohol prohibition is that you could prescribe alcohol for medical purposes in the United States, which created a very large and lucrative business for certain unscrupulous members of the medical profession. That might be one of the risks, I suppose, of continuing the prohibition on making cannabis available for therapeutic uses. I think it would be less of an issue for synthetic forms of the drug. There might still be some risk of diversion of use for recreational reasons. We see that with therapeutic substances now, but I think that might be something we would be prepared to tolerate in return for the benefits that would accrue to people who use the drugs for therapeutic reasons.

*Lord Soulsby of Swaffham Prior*

762. Can I ask one question with respect to Australia and the different ethnic groups, for example aborigines? Is there a problem with them, or can they handle cannabis better than the main population?

A. There certainly is growing concern, within the aboriginal population particularly among older adults, about cannabis use. A lot of concern is still, understandably, focused on alcohol, because in terms of the damage that is done there is no doubt that the damage caused by heavy alcohol consumption in those communities far outweighs the damage done by cannabis. What we see with cannabis in this population is what we see with alcohol. It is not a matter of a couple of convivial joints after dinner, it is very heavy use, usually in addition to alcohol and other substances. I think, in those circumstances, it certainly has undesirable consequences.

763. So your earlier comments about dosage and dependence might have to be altered considerably in the case of, say, its use by aboriginal people?

A. I think the other group we all ought to be concerned about is young people, particularly adolescents who initiate cannabis use in their early teens. They are a group which seems to be particularly likely to get involved in exactly the same pattern of very heavy use. I think we ought to be concerned about that, regardless of ethnicity. We certainly see that amongst young people, particularly those involved with the juvenile justice system in Australia: very heavy use of cannabis with adverse consequences for their personal development and their well-being.

*Chairman*

764. That is a relatively small proportion of the total number of users?

A. Yes. You are talking about, probably, one or two per cent of adolescents who get involved in that very heavy pattern of use.

*Lord Nathan*

765. I was going to ask you about a very interesting point which you raised relating to recreational and medical use. If the medical use was confined to THC or other cannabinoids which might deter leakage from the medical to the recreational field, would that allay some of your concerns? Would these products be attractive from a recreational point of view, or not attractive?

A. I think they would be much less attractive to cannabis users than smoked cannabis. The oral route of administration is one that a lot of cannabis users experiment with but very few persist in using. For example, in some 400 very long-term cannabis users we have studied I think there was one who was a regular user by the oral route; almost all of them had experimented with it at some time but they much preferred to smoke the drug in order to control the dose and the immediacy of effect. Synthetic cannabinoids would be much less attractive, and, given the ready availability of the cannabis plant product, it would be very unlikely that cannabinoid

30 September 1998]

PROFESSOR WAYNE HALL

[Continued]

Lord Nathan *contd.*]

extracts would have much recreational value. They would have some but I think it would be fairly minimal.

766. That is interesting, because one of the points which has come to us in evidence is that certain people—for example multiple sclerosis sufferers—seem to feel that cannabis, as opposed to any of these extracts or distilled versions of it, has an effect which is to be preferred. So that from that point of view they would say, I think, that cannabis in its original form was more attractive to them medically. So this would conflict with the idea you were just exploring then. Would you share that view?

A. Yes, that has been an issue, particularly as used for anti-emetic purposes as well. It is hard to know. There are two explanations often offered. One hypothesis is that cannabis products—plant products—contain not only THC but a variety of other cannabinoids that modulate the impact of the THC. The other would be that it is simply a route of administration effect. I do not know that we can

decide between those. I do not know if the evidence is in on that. Certainly it is much harder to control the dose by the oral route, and I think there has been a lot of interest in finding alternatives to smoking as routes of administration of the drug. That includes some of the advocates of legalisation, who recognise that there really are adverse consequences of smoking the plant product, but I am not aware of anyone who has come up with an alternative way of administering the drug that produces an effect equivalent to that of smoking.

*Chairman*

767. We have quizzed you for long enough, I think. We are most grateful for all your help and we thank you very much for sparing us the time.

A. It has been very interesting, as always, to discuss these issues with such a very well informed group as you obviously are. You have thought about this for some considerable time. Thank you.

#### Examination of Witnesses

PROFESSOR SIR WILLIAM ASSCHER, Chairman of the Royal Pharmaceutical Society working party on therapeutic uses of cannabinoids, PROFESSOR TONY MOFFAT, Royal Pharmaceutical Society, convenor of the working party, and DR ANITA HOLDCROFT and DR JOHN ZAJICEK, members of the working party, were called in and examined.

*Chairman*

768. Sir William, we are most grateful to you for giving up your precious time to tell us about your plans and also for bringing all your colleagues. Perhaps you could begin by introducing them to us?

(*Professor Sir William Asscher*) I will with pleasure, Lord Chairman. To my right is Dr Anita Holdcroft. She is a reader in anaesthesia at the Imperial College of Medicine, practising at the Hammersmith Hospital, Du Cane Road. On my left is Dr John Zajicek, who is a consultant neurologist in Derriford Hospital and his speciality *de la maison* concerns multiple sclerosis, as you will discover. To my extreme left is the man who is really responsible for all of this, and that is Professor Tony Moffat of the Royal Pharmaceutical Society and he is a professor in the School of Pharmacy in the University of London. I myself have got involved in this as a non-expert chairman of this group, having been asked by the BMA to do this job because I am the chairman of their Board of Science and Education for the next few years. That is how I have got involved and any technical questions will have to be addressed to them—that is why they are here. I was quite insistent I had some help!

769. Thank you very much. Could you tell us what the current progress on the plans for clinical trials is?

(*Professor Sir William Asscher*) We have held two meetings of this working group—on June 18th and August 11th—and in our first meeting we determined the objective of this group of the Royal Pharmaceutical Society, namely, to produce guidelines for pilot clinical trials for cannabinoids as proof of principle of their effectiveness and to assist

those who wish to conduct such trials to complete them successfully and publish the results. In our meeting we were quite insistent we would have no involvement in the development of drugs, merely proof of principle, so that the drug industry would have to take it up from there on, once we had proof of principle. We also were determined that we would be very focused and that is why we chose only two areas in which to design trials, namely post-operative pain and spasticity in multiple sclerosis, hence the presence of Dr Holdcroft and Dr Zajicek here today. The present situation, my Lord Chairman, is that the protocols are now with outside referees who will look at them for us, and their comments will hopefully come back to our next and last meeting, on October 21st, when we hope to finalise them and also to make arrangements for a launch of these protocols so we can interest potential investigators to carry out these trials. We have also, as a committee, looked at possible sources of funding. We had the benefit of the presence on our committee of a member of the Multiple Sclerosis Society and we know that there could be financial support forthcoming for the multiple sclerosis trials. We also had a member of the Medical Research Council present at our meeting, Dr Imogen Evans, and she has promised fast-tracking of any applications to the MRC and through them to access NHS R&D funding. Also, as chairman of the Board of Science, I am pleased to say that the Board of Science decided at its last meeting to dedicate its Joan Dawkins funds to cannabis trials in the coming year. That amounts to a reasonable sum of money which may help.

770. I understand that you will be using a number of different consultants to carry out the trials. Who is going to put the whole thing together?



30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued]

Chairman *contd.*]

(*Professor Sir William Asscher*) Our two lead consultants, are sitting to my right and left. Perhaps they would like to respond to this particular question themselves.

(*Dr Holdcroft*) My own particular trial is in acute post-operative pain. I am a consultant anaesthetist and this is the area in which I have most expertise. The study that we hope to do will focus on two types of major surgery, in other words the type of surgery that provides severe pain if we do not treat it effectively. So we would give a capsule, either placebo or THC or the natural preparation, pre-operatively and then study patients for six hours post-operatively. In order to get enough patients recruited and to do it in a reasonable time frame, we need at least two centres because my own hospital would not provide enough patients. We need something like 40 patients in each group, 240 patients in all, that is what we have been told by our statistician, so we plan to do it at least in the Hammersmith Hospital and at Northwick Park and maybe further afield, depending on how many people show interest. The Pain Society and our Royal College have also been involved in trying to define which centres would be best.

(*Dr Zajicek*) I am a neurologist with a special interest in multiple sclerosis and have been trying to co-ordinate multiple sclerosis research amongst neurologists in the UK. The number of patients required for a proper cannabis study, judging by our statistician, is approaching 600, so we will need a large multi-centre study in order to get sensible results. We estimate at least 25 centres will need to be involved in this and there are sufficient neurologists and sufficient patients to take part in such a study.

771. Can you tell us how close you are to getting, first of all, Home Office licences, secondly the CTX from the MCA and, thirdly, local ethics committee approval?

(*Professor Moffat*) What we would need for Home Office approval is the completed protocols. As Sir William has said, and what we want to do at our next meeting, is to finalise those protocols and then we would engage the clinicians at the launch and it is they who would then apply for the Home Office licence. If it was possible that Dr Geoffrey Guy was going to be one of the suppliers of the material, it is possible his Home Office licence might be extended to include this trial, but otherwise one would be obtained. I do not think we would get a CTX from the MCA, it would probably be a DDX, as they are much easier to get and I think this trial is probably small enough to do that. Both of those I do not regard as very much of a problem. The timescale we are looking at is probably not starting this trial for about nine months or so—that would be a reasonable length of time—so Home Office and MCA approval will be obtained relatively quickly. For the local ethics committee, once again, although it is a multi-centre study, that would be for my colleagues who are clinicians to put that through the relevant ethics committees. It would be a national trial but I think the local ethics committees would be asked as well. One thing which we were discussing at lunch is the possibility of indemnification insurance, and that will probably be left to each hospital or trust, or whatever it is, or we might have to consider

taking out special insurances. As regards the initial funding, as Sir William said, the Multiple Sclerosis Society are very keen, if they think that a trial is suitable, to consider the funding of that. We have an observer on our working group from the Medical Research Council who has already proposed to their Board that this be fast-tracked. That does not guarantee funding, only that it would be ready for perusal when it is ready.

772. You mentioned Dr Guy as one of the possible sources of supply. Have you got alternatives to that?

(*Professor Moffat*) Yes, there is a Dr Gorter in Germany who also has offered exactly the same as Dr Guy has—that they will provide all the materials which we want for the capsules of the standardised cannabis material. We would obtain the proprietary tetrahydrocannabinol from Cambridge Laboratories because although it is not a licensed product in this country. It is available in the United States. Sigma, the chemical company, unfortunately cannot supply it to us because they get their tetrahydrocannabinol from illicit sources in Israel. I say “illicit sources”—originally they are illicit sources, they are seized by the police and then they are provided to a chemist in Israel. However, they say “I am sorry, we cannot supply because the police have been so successful that there are no large seizures over there”. The last place that we could try (not in order of precedence but the last one I am mentioning) is the School of Pharmacy. It is they who provided the clinical trials material that Dr Holdcroft used in conjunction with Professor Evans. They have also supplied a limited number of trials materials for another trial. The size of the two trials which we envisage here, I think, are such that it is most likely that Dr Gorter or Dr Guy would be the suppliers.

773. You know that the THC content will be standardised, but what about the other cannabinoids?

(*Professor Moffat*) We decided that what we wanted to know, initially, was “Does tetrahydrocannabinol itself do the business or not?” That was the parallel stream. In order to answer the question “Is there anything in cannabis which does the trick, which may not be THC?” we decided to use an extract which could be reproduced, and we will standardise it on THC content. The proprietary preparation will contain, say, 5mg of THC and, also, the cannabis extract preparation too. But we will also assay all the other materials for which we have standards in that extract as well, so that we would know what is in there, first of all. Because we do not know what it is that is going to do the trick—what is going to be psychoactive. Also, there may be other materials in there which assist drug delivery and which, apart from being pharmacologically active, may just assist the process by which the body takes up tetrahydrocannabinol. So it is very important that we store those materials so that we can always go back to them and re-analyse them. However, they will be analysed in the first instance.

774. How many substances are you going to analyse first?



30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued]

Chairman *contd.*]

(*Professor Moffat*) About five or six of the predominant ones which we know about.

*Lord Dixon Smith*

775. We have had some evidence—I suspect it is anecdotal—that different sources of cannabis produce different effects. You would expect that. Obviously, the proportions of cannabinoids within the individual plants vary depending on where they come from. It is jolly fine relying on Dr Guy but supposing he actually has hit the wrong source for the purpose?

(*Professor Sir William Asscher*) He has his own farm and a licence to grow cannabis. Do you know, Tony, how standardised his product is likely to be?

(*Professor Moffat*) It will be standardised very well, but you are quite right, it could be the wrong thing. Our philosophy (and let me just say this is for United Kingdom, not imported, material, and I am also talking about plant material, not resin) is that the apocryphal stories that we hear are that people are growing their own material in this country and using that, and it is that which works. So our philosophy is, let Dr Guy do the same sort of thing, only licitly this time, with Home Office licensing and a Home Office Inspector there, and try and mimic what those patients were getting in the first place. That does not mean that cannabis plant material might not be active, it could well be that other studies are necessary. So this was our philosophy: let us try and mimic what other people have already done.

*Lord Porter of Luddenham*

776. I take it the fields of cannabis would be cloned, they would not be sown?

(*Professor Moffat*) The ones which he has under his greenhouse at the moment are all sown.

777. Sown?

(*Professor Moffat*) It is his intention, however, to clone them, so that he gets the same thing all the time. He will get the clones, I think, once he has established what it is that he wants. After all, he is in the same, or even worse, cleft stick that we are, because whatever he comes out with has got to be the right thing, and he has got to be able to reproduce that. So you are right in assuming that only by cloning can you genuinely reproduce that, but he does not know what it is that he needs to reproduce yet. Consequently, all his cloning experiments are being done in Holland and he has not yet done it in this country.

778. So it is going to be rather a long time before he has decided. If he can do it by cloning, that is okay, but if he is going to sow it, it is going to take a long time to see what the effective ones are.

(*Professor Moffat*) He has got something like 10 parallel streams and experiments with those to determine which is going to give him the greatest effect—and, of course, in each different disease state. Because the compounds are acting in different ways in those different disease states, each cannabis strain or plant may, in fact, be quite different depending upon that. He is in for a lot of fun, I think.

*Lord Butterfield*

779. How are you going to blind the psychoactive effects of cannabis and THC in your trials?

(*Professor Sir William Asscher*) That is difficult to do, my Lord, but can we take the two trials separately and ask Anita how she is going to do it, because her problem is less serious than Dr Zajicek's.

(*Dr Holdcroft*) I would like to widen the question, really, in terms of how you blind it altogether. As an anaesthetist, I am very much concerned that patients may become hypertensive, or tachycardiac if they are receiving the active preparation. On the other hand, if they receive a placebo they may also become tachycardiac prior to surgery. So I think that problem may even itself out. We have chosen a dose which is 10mg of THC, that in previous studies has not shown any moderate or severe psychoactive effects. It is the 20mg dose that shows those effects. This is based on Noye's study of the analgesic response in terminal cancer patients. His patients tolerated 10mg, and although I only examined one patient the 10mg dose did not produce in my patient any particular reactions that would worry us. I am more concerned about the cardiovascular effects than I am the psychoactive effects. We were discussing this beforehand, and I was saying that in anaesthesia we have a number of drugs that already have psychoactive effects, so it is a side-effect that we are used to working with. I will not say our patients go psychotic after anaesthesia, but we do see drug reactions with other groups of drugs.

(*Dr Zajicek*) I think this issue is one of the major reasons there has not been a study of cannabis in multiple sclerosis up to now, because there is not really a decent control we can use to control for the psychoactive effect. So, rather than try and control for it, we have said we will go for placebo capsules and then test the degree of blinding after the study. So we are aiming to run a study as a double-blind study and, obviously, assess whether the patients get psychoactive effects on the drugs. It is interesting to note, however, that previous studies of cannabinoids have actually shown psychoactive effects on a placebo preparation. So how much of a problem that is going to be is uncertain at the moment.

780. I am full of admiration for your approach, which I am sure is the only one you can adopt. It, very irritatingly, is what the technicians used to call "suck it and see".

(*Professor Sir William Asscher*) Yes, absolutely right.

781. From your minutes it appears that you see measurement of blood levels of THC and other cannabinoids as optional, rather than essential. We wondered why you thought they should be optional. Why are they not going to be done as part of the control investigation?

(*Professor Sir William Asscher*) I think that throughout the deliberations of our group we abided by the KISS principle—"Keep It Simple-Stupid". That is one argument for not measuring blood levels but there are others.

(*Professor Moffat*) The work which we have seen in the literature indicates that blood levels of tetrahydrocannabinol do not correlate with the



30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued]

Lord Butterfield *contd.*]

activity which is seen, certainly in terms of psychoactive activity. We are looking at fairly acute situations—over 24 hours, 48 hours—and also long-term in multiple sclerosis, and there is no evidence I have seen in all the pharmacokinetic literature that blood levels are worthwhile. However, there are two distinct places where I do think it has a place. The first is in determining whether patients are already on cannabinoids or, whilst they are taking placebos, whether they are taking cannabinoids on the quiet. I do think it has a place there. Secondly, we have been discussing this but have not come to a firm conclusion yet, the question is, is the tetrahydrocannabinol in the proprietary preparation different in bio-equivalent terms from tetrahydrocannabinol in a plant product which may contain other materials which would assist either the degradation of that material or, alternatively, it is facilitation across the barriers. So it might be a different equivalence. If there are bio-availability problems, it would be good to do that study up-front, but I guess we have not quite come to a decision about that. But we do not believe the monitoring of blood levels to relate to pharmacological effects is not a useful exercise for tetrahydrocannabinol.

782. What about taking samples and storing them so you can go back to them?

(*Professor Moffat*) We could do that but, for example, in the patient who has just had an operation, we are looking at post-operative pain, they are on morphine, we have given them tetrahydrocannabinol, and the thought of sticking needles into them does not really appeal very much; either to us or to them.

Chairman

783. Do they not have a line in anyway?

(*Dr Holdcroft*) We have written in a proviso that if they do have a cannula we would put it in the ethics form that we would take a blood sample and store it. Again, our problem is that in the analysis of the cannabinoids in blood it is quite difficult to separate them out as specific ones. Often people have looked at them as a group but we are hoping that in patients who do have cannuli in that they will give us permission to take blood samples.

Lord Butterfield

784. I hope you do not think it is cheeky of us to be probing like this before you set off.

(*Dr Holdcroft*) Blood concentrations are something to be considered.

Lord Porter of Luddenham

785. My Lord Chairman, I find the lack of correlation between THC and psychoactive effects very puzzling. Can you interpret this in any other way than that THC has no psychoactive effect?

(*Professor Moffat*) If I can give an example of somebody who is smoking: what you will get over the ten minute period they are smoking is the highest blood levels. Over the next two hours it will go away

from, say, 20 nanograms per mil to 1 nanogram per mil. The psychoactive effects will last maybe for eight hours. So you will get the psychoactive effects going up while the THC levels come down. If you do that multiple times it becomes even more complicated. So if you relate the series of psychoactive highs against the blood levels, that is why it does not correlate. For example, in smoking, you are getting it into the bloodstream very, very quickly and it is taking some time to get into the brain.

786. And out of the bloodstream quickly?

(*Professor Moffat*) Out of the bloodstream into the brain. Of course once it is in the brain, because this material is so lipid-soluble, it can remain there for days if not weeks, and you can detect cannabinoids in the urine of somebody who smoked one reefer cigarette containing 10 mg of tetrahydrocannabinol for three weeks afterwards; it takes a long time to come through the body.

Chairman

787. Can you explain briefly for us the endpoints you are proposing for the trial in spasticity?

(*Dr Zajicek*) The primary endpoint will be a change between the placebo group and the active group in something called the Ashworth scale. This is a scale of spasticity which is a very simple scale ranging from zero, meaning completely normal, to four, when the muscle group is very rigid and immobile. We will be using a number of different muscle groups based on previous trials of spasticity. There was a recent trial of a drug known as tizanidine, which is the most recent anti-spastic agent to come on to the market, and much of the trial design is based on that previous study. They found that there was a 10 per cent, more or less, difference between the placebo and tizanidine groups based on the Ashworth scale, and we will be using the same scale. There will be secondary endpoints and we are trying to cover as much as possible without making the trial too complicated. So we will certainly be looking at pain, mobility, disability for the patient in terms of what they can do with their arms and legs, urinary disturbance and so on as well as quality of life. So there are a number of secondary endpoints, but the primary endpoint will be spasticity on the Ashworth scale. There is a device, costing several thousand pounds, which is said to measure spasticity based on a pendulum effect, so someone hangs their knee over the end of a bed and you measure how it swings, and a small sub-group of patients will be used to assess this device. This is something which Exeter University are interested in at the moment.

Lord Soulsby of Swaffham Prior

788. Coming to endpoints again, with respect to analgesia you have chosen acute post-operative pain rather than chronic pain, and also you have chosen morphine substitution as an endpoint. Can you explain why you have made those decisions?

(*Professor Sir William Asscher*) Chronic pain was not cast out by the committee, it was a question of having somebody who was very expert with acute pain on the committee and who was willing to do the



30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued]

Lord Soulsby of Swaffham Prior *contd.*]

work. As it happens, I must be totally frank with you, when I came up on the train to the first committee meeting and thought that almost certainly the committee was going to choose spasticity and chronic pain in terminal cancer patients as their protocols. In fact acute pain was something which was probably preferable to do in the circumstances because it would give quicker results. Let me hand over to Anita to give her reasoning, but she persuaded the committee that her proposal was the right priority.

789. I suppose it is just a question of numbers really?

(*Professor Sir William Asscher*) Yes, it was a question of availability of patients; and the particular interest of Dr Holdcroft but the availability of patients above all.

(*Dr Holdcroft*) I have run a chronic pain clinic for five years—I do not run it at the moment—so I am familiar with patients with chronic pain. They have often got other associated conditions so it is quite difficult to get a “clean” group. If we believe that cannabis or THC is an analgesic the best acute model is in acute post-operative pain, and then within that you define which particular groups you are going to look at. Then you define the strength of analgesic required for that type of surgery for cannabis or THC, we really are basing our knowledge on Noye’s study, which demonstrates activity similar to codeine. When you study post-operative patients, you have to be able to give them an analgesic to match their pain—you cannot give a placebo, with no pain relief, for somebody who has had an operation. Morphine is our gold standard for analgesia. What we do find is that when we use a drug in the broad group of non-steroidal drugs, like diclofenac (voltarol), which is a modest analgesic and an anti-inflammatory, we can reduce the amount of morphine that we give patients. Based on that principle and based on the results of many other studies which have used morphine consumption as an endpoint which is quantitative—it is not one of these qualitative measures like how much pain have you got—we plan to use that as our primary outcome measure. So, for the immediate post-operative period, about four hours after surgery, we can use patient-controlled analgesia. This will contain morphine, and then we can measure the amount of morphine they have used in the different groups and work out, on a number basis, whether there is any difference. We will also be measuring, on a qualitative basis, using a visual analogue score, how much pain they have. However, I am a clinician, I have to deal with patients and I do not want them to be in pain afterwards. So if you are running a placebo group you have to have something that is going to give good relief in that group and also assist, maybe, to supplement the cannabis that we are giving them in the active group. Morphine consumption is a good endpoint, it has been used very frequently in acute pain studies and we have based our statistics on a reduction in morphine dosage similar to many other recent studies.

790. Thank you.

(*Professor Sir William Asscher*) Now you know why we were persuaded by Dr Holdcroft, my Lord.

Lord Dixon Smith

791. If I understand matters correctly, you are going to be trialling using a standard dose, in order to help produce a standard outcome. However, we have heard in evidence from those who use cannabis to relieve symptoms in MS that one of the reasons why they like to use it is because they can regulate their dose very easily and very quickly, and as soon as they have got the effect they just stop. So they will not necessarily need to smoke a joint, perhaps just three or four puffs and that is it. Will your trials involve an element of self-titration by the patient to allow for this effect? Or are you going to stick with the standard dose in the first instance?

(*Dr Zajicek*) We will be aiming for a standard dose of 0.25mg per kilogramme—so, approximately, 10mg twice a day depending on body weight. There will be a four-week titration phase where the patient will be reviewed twice. During that time the patient and the physician will decide whether to increase the dose of the drug, depending on the effect and any side-effects of the drug. So there will be a titration of sorts, but it will be a controlled titration so that we are able to adjust for it, although we are aiming for a specific dose.

Lord Porter of Luddenham

792. May we ask you for a little more information about the timetable of your trials? First of all, when will they begin?

(*Professor Sir William Asscher*) I think it is entirely determined by the availability of the materials, assuming that we reach a conclusion on the final protocol on 21 October. I think, Tony, you mentioned earlier July 1999 will be the sort of timing we are looking at.

793. It could really be a bottle-neck, the supply of materials?

(*Professor Sir William Asscher*) Yes, the supply is the limiting factor here.

794. Supposing they do begin, how long are they intended to take? How long might it take then to analyse and publish the results?

(*Professor Sir William Asscher*) I am going to refer that question to the trials leaders. Anita, in the case of pain, how long do you think we will take?

(*Dr Holdcroft*) We hope, clinically, a year. It obviously needs a set-up time and then time to analyse the results afterwards. Again, if we had multiple sites we may be able to reduce that time period. In all between 18 months and two years before we have the final results.

795. Including analysis?

(*Dr Holdcroft*) Yes.

796. That is not unreasonable, I should have thought. If either trial, in the two areas that you have told us about, shows cannabis itself to be effective and more effective than dronabinol, how long might it then take for a licensed medicine to be available?

(*Professor Sir William Asscher*) That is the worst-scenario, because it might be difficult to persuade researchers to tease it out, as it would be an expensive, lengthy, tedious and difficult task. I



30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued]

Lord Porter of Luddenham *contd.*]

wonder whether any pharmaceutical company would be prepared to take it on, I doubt it. There would have to be a lot of investment, as Professor Iversen will, no doubt, verify. It is a very difficult situation, because you will not get a product with 64 different cannabinoids licensed—not in this country—not knowing which one is the active compound.

797. So we cannot look forward with any confidence to anything in the near future?

(*Professor Sir William Asscher*) My view would be that if the results were as you indicate, that a capsule works and the THC does not, it would mean a lot more work needed to be done before we have a licensed medicine. If they both work it is an easier proposition, of course, because THC is prescribable anyway—certainly in the United States. If THC only works that is also fine. But the scenario you paint is the one that we all dread. Is that not right, Tony?

(*Professor Moffat*) From the time that the results are published to the time that we could expect to see a licensed product, five years would be very fast, seven years would be reasonable, and it may take beyond that. I think what we could look forward to—just expanding on the question a little more—is if the tetrahydrocannabinol works then because the product exists in a licensed form in the United States it is quite possible to bring it in with its own portfolio of licensed material from the Food and Drugs Administration. You could get that licensed for use in this country very quickly. Even so, it is still able to be prescribed by GPs now, of course, but they are wary because they do not know the clinical relevance of the material and they can prescribe it on a named patient basis. Even so—let us suppose the standardised material was available and the drug was not available—it could still be released for use by a manufacturer for use by patients providing the law was changed. I will not pre-empt that question, I will wait till later. But if the law was changed it would mean that a preparation which was proven by clinical trials to be therapeutically effective and it could be prescribed by GPs.

Lord Kirkwood

798. The outcome might be that the cannabinoid was effective but not as effective as the natural drug. What situation would that produce? Presumably, it would mean there was more research, but, in the meantime, it would be possible to prescribe the cannabinoid.

(*Professor Moffat*) Exactly so. That is right. As I said, the law would have to be changed because cannabinoids are currently Schedule 1 and they would have to move to Schedule 2 to allow their prescribing. However, what you would know is whether the natural preparation was more active than THC, and providing that it was reproducible it could be prescribed during that period of time. The aim must be to have a known product which is stable, etc, and be a licensed product. That is where it will end.

(*Professor Sir William Asscher*) It is an unsatisfactory situation, my Lord, because if you do not have a licensed product you have no post-marketing surveillance, and you have no idea, really,

what adverse effects that drug produces. You get no yellow cards in. It is not a very satisfactory situation to be in to provide cannabinoids on a named patient basis.

799. [Unallocated]

800. [Unallocated]

Lord Butterfield

801. I wonder if you could help us by telling us the relationship between the work you are doing and the work of Geoffrey Guy.

(*Professor Moffat*) Yes. What we have done is kept in very close contact. I have spoken to him twice by E-Mail and conversed with him over the telephone. I do not think he is yet ready to conduct clinical trials, whereas what we would like to do is get them under way. However, he has offered to provide material for us and I think, as such, he would then be a collaborator within our clinical trials and will be providing the material for us.

802. Not “the” material, “a” material? Or “the” material?

(*Professor Moffat*) I am not quite sure what they would be. It depends who provides what at what time, and the timescale. If I can say, the great advantage that Dr Guy has over everybody else is that I can see in the years to come that whatever material he might make available to us will be reproducible. This goes to my Lord Lord Porter’s question about cloning and reproducibility. Looking forward then, he offers the best bet for the provision of the materials.

803. So if he can produce something that is pretty reproducible, you will not go looking at that German source? You will stick to him probably?

(*Professor Moffat*) I think that has to be discussed by the working party as a whole.

804. Okay, but that is not impossible?

(*Professor Moffat*) Yes, that is correct.

Chairman

805. Are you aware of any other clinical trials, apart from your own and Dr Guy’s, which are taking place currently?

(*Dr Zajicek*) I can talk about a trial in multiple sclerosis which is planned with Exeter University. I spoke to the investigators yesterday about how far on they are. They are having trouble with getting a supply of the drug and they are, as I explained earlier, using a machine to try and assess the degree of spasticity, so they are really looking at using 20 or 30 patients on a small scale. They will be very keen to join in the national study which we propose from the working party and then to analyse a sub-group of those patients with this pendulum machine. So we hope to work together in the future.

806. That is of standardised cannabis?

(*Dr Zajicek*) At the moment they are planning a separate study but after communication they are keen to take part in the national study which we propose, placebo against cannabis oil against THC.

30 September 1998]

PROFESSOR SIR WILLIAM ASSCHER, PROFESSOR TONY MOFFAT,  
DR ANITA HOLDCROFT AND DR JOHN ZAJICEK

[Continued

Chairman *contd.*]

(*Dr Holdcroft*) I know of a study that Dr Claire Fowler at Queen's Square, the Institute of Neurology, is proposing to do on bladder spasticity rather than just skeletal muscle spasticity. Again, she has quantifiable endpoints such as the capacity of the bladder before and after cannabis use. The main problem for her at the moment is the paperwork but the cannabis material may come again from Dr Guy for that particular study.

Lord Nathan

807. May I ask whether you have knowledge of clinical trials in this area going on elsewhere than in the United Kingdom? There seems to be a growing, intensive concern with regard to the use of cannabis for medical purposes, or THC and so forth, and it would be surprising to me if there were no activity elsewhere.

(*Professor Sir William Asscher*) We are aware of some, Lord Nathan. You have been trying to get in touch, have you not, Anita?

(*Dr Holdcroft*) Yes. We do believe in Virginia (USA) that there is a group looking at chronic pain. This was one of the other reasons why we were not pursuing that further at the moment. We are trying to get some information back from them. As far as I understand it, they are using THC and not the natural product but they are certainly studying chronic pain.

808. Of course one has to have regard to the international conventions but the Government could, in theory, transfer cannabis from Schedule 1 to Schedule 2 in advance of the outcome of your trials so as to permit medical use, albeit on an unlicensed and named-patient basis. On the basis of what you already know, would you regard this as justified or premature?

(*Professor Sir William Asscher*) My personal answer to that would be that by so doing you would probably endanger future trials, proper trials, because inevitably people are going to be using it and you will accumulate a very large series of anecdotes to say how good it is without actually knowing whether it is good. I think it would probably be premature to do this at this stage. You should allow some focused work to be undertaken and then see that it is done. I do not know how long it takes to re-schedule a substance like this but if it takes a very long time perhaps you could make all the preparations and wait for the results of the trials before the final decision is made.

809. One of the things that certainly impressed me was the evidence we received in relation to multiple sclerosis, that it was felt not on any detailed scientific basis but by those who suffered that the use of cannabis as opposed to THC or medicines derived from it had a beneficial effect. So what one would be doing by the deferral to which you refer, for reasons which I fully understand, would be to deny to the MS sufferers a source of relief which they think, rightly or wrongly, is good for them. What do you feel about that?

(*Professor Sir William Asscher*) Of course, the perception is as good as the real thing but not to a scientist.

810. Quite.

(*Professor Sir William Asscher*) I suspect that there are ways and means for these people who find it so beneficial to continue to have those benefits without re-scheduling. Re-scheduling would, I think, endanger future trials and that is what we are trying to do and would actually interfere with the good work being done. I am not sure everybody from my side agrees there may be other views. I know the Pharmaceutical Society has a different view.

(*Professor Moffat*) The Royal Pharmaceutical Society takes the view that it would be very useful if doctors had the ability to prescribe cannabinoids in the meantime while trials were going on, but I do believe it is a balance. Everything Sir William has said is absolutely right, if the material was available then why would multiple sclerosis sufferers bother taking part in a trial where they might get a placebo when they could get it from the doctor? On the other hand, the doctor is not going to be able to prescribe anything at all unless it becomes available and we are trying to get in the end a licensed product which would truly be for the benefit of patients. It is this long-term gain versus short-term gain which is very difficult. That is why we sit here and you gentlemen sit there!

Chairman

811. We are extremely grateful for your patience in answering our questions. Thank you very much indeed.

(*Professor Sir William Asscher*) Thank you for listening so attentively.



### Memorandum by the Association of Chief Police Officers

1. A research project by the Association of Chief Police Officers (ACPO) Crime Committee, Drugs Sub Committee, considered various issues relating to Cannabis. Evidence was gathered from various sources, some of which addressed the issues being looked at by the Select Committee. The following is a summary of that evidence, its sources and the conclusions reached. It is based on pages 6 to 10 of the ACPO Response to the Independent Enquiry into the Misuse of Drugs Act 1971. Appendix "A" details a document by the World Health Organisation which was not used in the ACPO Response, but which the Select Committee may wish to consider.

#### 2. *Physical Effects of Cannabis*

2.1 Joseph Canepa<sup>1</sup> describes the physiological effects of Cannabis as:

"A low to moderate dose of Cannabis produces a subjective sense of well-being, with relaxation, drowsiness, mild perceptual alteration, altered sense of time and distance, impaired recent memory and impaired coordination, particularly during complex perceptual motor tasks. The intoxication peaks 15 seconds after inhaling the smoke and lasts, at least, in an objectively measurable way, for two to three hours after a single cigarette".

2.2 Canepa goes on to detail the physical effects of Cannabis and its main psychoactive molecule, Delta-9-Tetrahydrocannabinol (THC). Interference with learning, memory, motivation, cognition and motor coordination have all been observed and consequent effects on tracking performance, glare recovery, depth perception, time sense, peripheral vision, reaction time and signal detection have serious implications for a safe driving, flying and machine operation. Impairment can last for 10 hours and the effect on reaction time and coordination appears to be amplified when Cannabis is used with alcohol.

2.3 In the longer term, Brett & Stoker<sup>2</sup> state that Cannabis appears to be more carcinogenic than cigarettes, can effect the immune system, fertility and cause smaller offspring who are more susceptible to one type of Leukaemia. They also state that the University of Mississippi has 10,500 scientific papers on Cannabis, none of which give Cannabis a "clean bill of health".

#### 3. *Psychological Effects*

3.1 Canepa<sup>3</sup> reports that pain, paranoid states, anxiety, confusion and acute psychosis can accompany the feelings of euphoria, sometimes attained by Cannabis use. He also states that use by those with a history of mental disorder can precipitate psychiatric symptoms. In addition "Amotivational Syndrome" has been used to describe observed changes in behaviour patterns, including apathy, difficulty in concentrating, emotional blunting, hostility towards authority and decline in work or school performance.

#### 4. *Cannabis as a Medicine*

4.1 The therapeutic use of Cannabis has been advocated for several conditions, the medical benefits reported to be:

- Increasing appetite in HIV+ and anorexic patients.
- Reducing nausea and vomiting following chemotherapy.
- Reducing intra ocular pressure caused by glaucoma.
- As an analgesic to reduce pain.
- Increasing muscle spasticity after spinal injury or for multiple sclerosis sufferers.

4.2 The British Medical Association conducted a survey of scientifically controlled trials of Cannabis and Cannabinoids to treat medical conditions. It concluded that "... although Cannabis itself is unsuitable for medical use, individual Cannabinoids have a therapeutic potential in a number of medical conditions, in which present drugs or other treatments are not fully adequate<sup>4</sup>".

4.3 The report stated that the unsuitability of Cannabis was due to its constitution of over 400 chemical compounds, including 60 Cannabinoids, their varying concentrations, the toxicity of its smoke, its possible adulteration during cultivation and processing, and its psychotropic activity.

4.4 The report called for further research into the benefits of Cannabinoids and suggested changes to the UN Convention on Psychotropic Substances, or the Misuse of Drugs Act, to enable the granting of further licences to facilitate this. Such a move should be viewed as the "medicinalisation" of Cannabinoids and completely distinct from decriminalisation or legalisation of Cannabis.

<sup>1</sup> Canepa Joseph Louis: Cannabis & Its Problems, page 6; Bramshill Police Staff College, 1986.

<sup>2</sup> Brett Mary & Stoker Peter: Thinking The Thinkable; Policing Today, volume 1 no 3, pages 13-17.

<sup>3</sup> Canepa Joseph Louis: Cannabis & Its Problems, page 8; Bramshill Police Staff College, 1986.

<sup>4</sup> British Medical Association; Therapeutic Uses Of Cannabis; Harwood, Amsterdam, 1997.

4.5 In the USA, many States have pending legislation to decriminalise the medical use of Cannabis, although the Federal Government has rejected such use. These proposed changes are driven by public opinion, rather than scientific research and different States put forward different approaches. For example, California proposes to make Cannabis available to all of those patients in need of it; Maine is considering that a defence to possession and cultivation should be that it was on the written recommendation of a licensed physician; other States are looking only to grant licences for research purposes.

4.6 In August 1997, the Dutch Health Inspectorate, acting on a report by the Dutch Health Council, banned the prescribing of Cannabis after concluding there was insufficient proof of its medical benefits<sup>5</sup>.

4.7 ACPO considers that if any controlled drug is scientifically proven to have therapeutic value, then its use should be supported under prescribed conditions. Furthermore, whilst cannabinoid compounds have a legitimate place in medicine, Cannabis does not.

## 5. Decriminalisation In Other Countries

5.1 When personal use of Cannabis by adults became decriminalised in Alaska, a number of changes were noted before its recriminalisation in 1991, a decade later<sup>6</sup>. This included a University of Alaska study that found that Cannabis use by minors had become twice the national average and had changed from being experimental in nature to becoming incorporated into the lifestyle of many adolescents. In addition, between 1988 and 1990, over 2,000 Alaskans were admitted to state funded drug treatment programmes, with Cannabis Resin as their prime substance of abuse.

5.2 Whilst in Alaska the results of decriminalisation are to a degree measurable, as they can be compared directly to the average for US states in the same period, data regarding Dutch decriminalisation is less easy to analyse. Much of what has been written has been subjective comment, since the various recording practices of different countries can make comparisons meaningless. Whilst there are undoubtedly positive aspects of Dutch drugs policy, particularly in the area of treatment, the cost of decriminalisation in social and health terms is unclear.

5.3 Figures from the Dutch Criminal Investigation Information Service show that between 1993 and 1995, seizures of Cannabis more than doubled and seizures of Nederweed plants increased more than other forms of the drug. Nederweed is an indigenous Cannabis, which supplies up to 50 per cent of the Dutch market and is especially strong. It has a Delta-9-Tetrahydrocannabinol (THC) content of up to 27 per cent, compared with the more common street Cannabis which contains 5–10 per cent. THC is the most potent psychoactive agent in Cannabis and the strength of this form causes increased side effects, and can bring on medical problems in the mentally ill more readily. Its use in Britain would appear, from Police seizures, to be increasing.

## 6. Driving

6.1 Many studies (eg Institute For Human Pharmacology, Netherlands<sup>7</sup>) have established that Cannabis use adversely effects driving ability. Although it is contended that these effects are not as marked as with alcohol consumption, it cannot be disputed that driving is impaired and accidents must, therefore, be more likely than when no substance is taken. Such impairment can also be expected when machinery or other vehicles are used.

7. ACPO believes that Cannabis is a harmful substance, the control of which must be continued. Its physical and psychological effects far outweigh any medicinal benefit and no concession should be given to medical usage. Therapeutic use of prescribed Cannabinoid compounds is a separate issue, and is supported where scientific evidence supports its value. Decriminalisation in other countries has provided no clear evidence of benefits of such a breach of International Conventions; it has been to the detriment of those countries in some respects.

## Appendix A

### The World Health Organisation "Cannabis: A Health Perspective Research Agenda"

1. This comprehensive document is not on release to the general public and, therefore, was not referenced in the ACPO Response to the Independent Enquiry into the Misuse of Drugs Act 1971. It reflects the position of International research into Cannabis in 1995 and may well be of interest to the Select Committee.

2. The report extensively analyses the acute and long term effects of Cannabis on the central nervous system and behaviour, including the capacity to operate vehicles and machinery and Cannabis Dependence Syndrome. The report also documents the effects of Cannabis on the respiratory system, the endocrine and

<sup>5</sup> British Medical Journal; Volume 315, Page 304, 30 August 1997.

<sup>6</sup> Calvert Simon: Decriminalisation of Cannabis—The Alaskan Experiences; Drug Bulletin Winter 1997–98 The Christian Institute.

<sup>7</sup> Zimmer Lynn & Morgan John: Marijuana Myths Marijuana Facts, page 126; the Lindesmith Center, New York, 1997.



reproductive systems, intra-uterine and post-natal development, cell nuclei, the immune system and other organ systems, as well as assessing the therapeutic potential of Cannabis.

3. In addition to the widely recognised acute effects of Cannabis, the report found that chronic use of Cannabis produced a number of additional health hazards, both physiological and psychological.

*Colin Phillips*

Chairman, Drugs Sub-Committee

**Memorandum by Dr Anthony Blowers CBE JP DL, Consultant (Drugs Misuse) Faculty of Education  
Roehampton Institute and Chairman of Surrey's Drug Action Team**

### THE PREVALENCE OF ILLEGAL DRUGS IN PSYCHIATRIC ILLNESS

"In the end it bites like a snake and poisons like a viper. Your eyes will see strange sights and your mind imagines confusing things." Proverbs 23: 32-33 Gideons Bible

#### INTRODUCTION

Lord Lane, a former Lord Chief Justice of England, writing the Foreword in "Drug Warning" (Stockley 1992), observed that if someone could stop the abuse of drugs tomorrow, not only would thousands of young people be saved from degradation and possibly death, but also one of the main causes for the upsurge in all types of crime would go.

Illicit drug trafficking accounted for approximately 8 per cent of all International trade in 1994, with an estimated value of £300 billion a year—a sum larger than the gross domestic product of Australia (World Drugs Report, 1997). This report estimates that there are 140 million cannabis users worldwide, and there has been a rapid increase in the numbers using synthetic drugs such as amphetamines and Ecstasy, thus making the problem a truly global one.

Poole and Brabbins (1996) suggest that drug use is a major complicating factor in psychosis, which renders the management of psychotic disorders more difficult. In collecting data on psychotropic drug abuse in 38 schizophrenic and 36 affectively ill patients consecutively admitted to a psychiatric unit, Weller et al (1984) found there was an excess of drug users in the schizophrenic group. Numerous studies have implicated cannabis as a complicating factor in schizophrenia (Andreasson et al, 1987; Traffert, 1978; Knudsen and Vilmar, 1984; Davidson and Wilson, 1972 and Breakey et al, 1974). In an on-going study results are reported of the prevalence of illicit drugs in patients detailed under the Mental Health Act 1983.

#### MATERIALS AND METHODS

##### *Study Population*

155 detained patients were seen during the initial study period of five years. 100 were seen in a total of 34 different psychiatric units (Group A), and the remaining 55 were seen in one unit (Group B), with a locked facility, that specialises in the care of difficult to manage patients.

##### *Information about Drug Misuse*

Medical records were examined for information on illicit drugs and further details were obtained during interviews. It is well known that drug misusers frequently understate their involvement in drug misuse (Miles, 1975 and Connell, 1958).

#### *Results*

##### *Group A (Table 1)*

Of 100 patients (59 males and 41 females), mean age 36.87 years, 48 (30 males and 18 females) 48 per cent, had a history of drug misuse. 39 (27 males and 12 females) 39 per cent, had a history of alcohol misuse. In the group who had a history of both drug and alcohol misuse, 24 patients (15 males and nine females) 24 per cent, were identified. Those who had a drug or alcohol problem or both, numbered 62 (41 males and 21 females) 62 per cent.

##### *Group B (Table 2)*

Of 55 patients (51 males and four females), mean age 28.93 years, 45 (42 males and three females) 81.82 per cent, had a history of drug misuse. 24 (23 males and one female) 43.64 per cent, had a history of alcohol misuse. In the group who had a history of both drug and alcohol misuse, 17 patients (16 males and one female) 30.91 per cent were identified. Those who had a drug or alcohol problem or both, numbered 52 (49 males and three females) 94.55 per cent.

*Groups A and B (Table 3)*

Of the 155 patients in the study (110 males and 45 females), mean age 34.05 years, 93 (72 males and 21 females) 60 per cent, had a history of drug misuse. 63 (50 males and 13 females) 41 per cent, had a history of alcohol misuse. In the group who had a history of both drug and alcohol misuse, 45 (36 males and nine females) 29 per cent, were identified. Those who had a drug or alcohol problem or both, numbered 114 (90 males and 24 females), 73 per cent.

Table 4 shows the breakdown of individual drugs in the 155 patients interviewed. Cannabis featured in 81 patients, followed by amphetamines misuse, being admitted by 35 patients. Cocaine was noted in 24 patients, Lysergic Acid Diethylamide (LSD) in 20 followed by ecstasy in 17. Heroin was recorded in 10 patients and crack cocaine in six.

## DISCUSSION

Results obtained in the first 155 patients in this study suggest a strong link between illicit drug abuse and mental illness. Many studies support this hypothesis and the various opinions are briefly outlined below under separate drug headings. The five most commonly used drugs in this study are considered. This situation may change as the most recent information (Drugs Forum Focus, 1997) indicates that heroin is now reaching epidemic proportions in some parts of the UK.

*Amphetamines*

There is considerable evidence to support the view that amphetamines can induce symptoms of a psychosis closely resembling paranoid schizophrenia (Connell, 1958; Ellinwood, 1967 Griffith et al, 1972). Biochemical, pharmacological and histochemical evidence suggest that amphetamines stimulate increased dopamine release in the CNS (Randrup & Munkvad 1966; Scheel-Kruger & Randrup, 1967; Christie & Crow, 1971). Phenothiazines have been shown to reverse the central effects of amphetamines in animals (Munkvad, Pakkenberg & Randrup, 1968; Christie & Crow, 1971) and in man (Espelin & Done, 1968).

Amphetamines have been used in rats to induce these effects thus producing an animal model that has been used in testing the potency of antipsychotics, before clinical trials in man are undertaken.

*Cannabis*

There have been many calls for the legalisation or decriminalisation of cannabis. One national newspaper has run a campaign in support of the use of cannabis therapeutically in certain indications where pain is a continuing feature. Claims have been made that the smoking of cannabis, even long term, is not harmful to health (Lancet editorial, 1995). A British Medical Journal Editorial (Smith, 1995) suggests that wars on drugs are doomed to failure, and that experiments with decriminalising and even legalising drugs have shown promising results.

The supporters of legalisation of cannabis tend to avoid the downside of cannabis use (misuse). In classifying the psychotic effects of cannabis under three headings, Rathod, (1975), described dose related acute psychotoxic reactions; idiosyncratic reactions; and other psychiatric disorders. Miller, (1975) referred to the claim by some that a "cannabis psychosis" exists whilst others deny that such a separate clinical entity can be established.

In a study involving 45,570 Swedish conscripts during a 15 year follow up, the relative risk for schizophrenia among those who used cannabis more than 50 times, was 6 times more than non-users (Andreasson et al, 1987). A later paper (Andreasson et al, 1989) in a small study of schizophrenics, observed that the findings supported the hypothesis that cannabis does play an aetiological role in schizophrenia.

Many other papers describe the psychiatric effects of cannabis (Talbot and Teague, 1969; Golbach and Crowe, 1970; Tennant and Graebek, 1972; Davidson and Wilson 1972; Chopra and Smith, 1974; Carney and Bacelle, 1984; McBride and Thomas; 1985; Ghodse, 1986).

In a recent review article Wickelgren (1997) suggests that contrary to the popular view that marijuana (cannabis) is a relatively benign drug, new evidence suggests its effects in the brain resemble those of hard drugs such as heroin. De Fonseca et al (1997) traced the symptoms of emotional stress caused by marijuana withdrawal, to the brain chemical corticotrophin-releasing factor (CRF), that has already been linked to anxiety and stress during opiate, alcohol and cocaine withdrawal. Tanda et al (1997) report that the active ingredient in marijuana, tetrahydrocannabinol, results in the same key biochemical event that appears to reinforce dependence on other drugs, from nicotine to heroin; a release of dopamine in part of the brain's "reward" pathway.



### *Lysergic Acid Diethylamide (LSD)*

The first systematic study of the clinical effects of LSD was carried out in the University Psychiatric Clinic in Zurich in 1947. In minute doses (0.5mcg./kg. body-weight) it was observed to produce changes in emotional behaviour, hallucinations, depersonalisation, and reliving the repressed memories (Sandoz, 1964). Reference is made to considerable individual variation with onset of action usually within 15 to 60 minutes. Effects usually pass off within 24 hours but adequate supervision is advisable. The foregoing relates to an era when the compound was used in analytical psychotherapy. LSD was used under "proper psychiatric supervision" and supplies were restricted to qualified psychiatrists. Under "precautions" psychotic episodes and severe depressive states are listed as possible adverse reactions. Model psychosis was described as being induced.

Following the manufacture of LSD in a number of mid-European countries and the widespread illicit use, Sandoz stopped all supplies (Blowers, 1997).

In a study comparing patients hospitalised with LSD psychosis with acute schizophrenics Vardy and Kay (1983), found that in most respects the LSD psychotics were fundamentally similar to schizophrenics in genealogy, phenomenology and course of illness. Their findings supported a model of LSD Psychosis as a drug-induced schizophreniform reaction in persons vulnerable to both substance misuse and psychosis.

Glass and Bowers, (1970) referred to the view expressed by many, that psychomimetic drugs are often thought to "precipitate psychotic reactions in psychosis—prone individuals". They put forward the view that the protracted use of certain drugs can produce a chronic psychotic adaptation in individuals whose premorbid histories are not typical of prepsychotic individuals.

In a report (Daily Telegraph 1997a) the Library of Congress have opened to the public the diaries of Clare Booth Luce, the former US Ambassador to Italy. These have revealed her use of LSD. She spoke of being afraid for her sanity in a "blood boiling brutal battle" involving the drug.

### *Cocaine*

Paranoid Schizophreniform psychosis similar to that associated with amphetamines has been reported (Griffith et al, 1972), particularly following long term use (Jaffe, 1970; Post, 1975). A tentative diagnosis of toxic cocaine psychosis was made by Lesco et al, (1983). The patient was presenting with hallucinations, delusions, pressure of speech and irritability. Hallucinations have been reported elsewhere (Siegal, 1978).

### *Ecstasy*

Publicity in the popular press and medical journals (Lancet, 1996) on the dangers of using Ecstasy, has been concentrated almost exclusively on the problems of acute toxicity. Green and Goodwin (1996) observed that so little attention is being paid to the long term effects of this drug. They pointed out that evidence has existed for several years that Ecstasy induces neurodegeneration by causing long term destruction of serotonergic axons and axon terminals in the brain. (Green, Gross and Goodwin, 1995).

Data from the Department of Health suggest that there are currently around 10 deaths a year in England and Wales where Ecstasy was the only drug involved (Postnote, 1997). The report suggests that this is an under-estimate. It also outlines two recent studies which strengthen concerns that Ecstasy use can affect the brain some time after the immediate effects of the drug have worn off.

Postnote (1997) presents details of current research by Morgan et al (1997) and Curran and Travill, (1997). Morgan et al (1997) found that Ecstasy users performed significantly less well in some of the neuropsychological tests, than those in the other two groups. Curran and Travill (1997) have produced evidence of short-term psychological problems related to Ecstasy use. The study found that users were significantly more depressed mid-week than they were at weekends, to the extent that some of the users qualified for a psychiatric diagnosis of depression at the mid-week assessment. Such effects are consistent with the neurochemistry where the drug provides a short-term boost to serotonin levels, followed by a depletion some time later.

Perhaps the most disturbing evidence comes from a study by Ricaurte at John Hopkins University, Baltimore (Daily Telegraph 1997b), who discovered that Ecstasy can trigger long lasting changes in the human brain. They confirmed earlier findings that Ecstasy users have deficiencies in the neurotransmitter serotonin, and using radioactive tracers they observed damage to serotonin synapses by PET scans. This is suggested as a knee-jerk reaction by drug opponents (*The Independent*, 1997) who state that "this is not controvertible evidence of permanent damage. The human brain repeatedly demonstrates that it is capable of withstanding massive amounts of damage and rebuilding itself". The same newspaper is currently conducting a high profile campaign to legalise cannabis.

The relatively low level of Ecstasy use (8 per cent) in the study is possibly explained in that the mean age of the total population examined was 34.48 years. The mean age of those taking Ecstasy was 25.77 years and is in line with the use of this drug in the younger age group.

Table 1

GROUP A PATIENTS (n = 100)

59M 41F MEAN AGE 36.87 YEARS

|                           | No. | Sex |     | %  |
|---------------------------|-----|-----|-----|----|
| History of drug misuse    | 48  | 30m | 18f | 48 |
| History of alcohol misuse | 39  | 27m | 12f | 39 |
| Drug plus alcohol misuse  | 24  | 15m | 9f  | 24 |
| Drug or alcohol or both   | 62  | 41m | 21f | 62 |

Table 2

GROUP B PATIENTS (n = 55)

51M 4F MEAN AGE 28.93 YEARS

|                           | No. | Sex |    | %    |
|---------------------------|-----|-----|----|------|
| History of drug misuse    | 45  | 42m | 3f | 81.8 |
| History of alcohol misuse | 24  | 23m | 1f | 43.6 |
| Drug plus alcohol misuse  | 17  | 16m | 1f | 30.9 |
| Drug or alcohol or both   | 52  | 49m | 3f | 94.5 |

Table 3

COMBINED GROUP A AND B PATIENTS (n = 155)

110M 45F MEAN AGE 34.05 YEARS

|                           | No. | Sex |     | %  |
|---------------------------|-----|-----|-----|----|
| History of drug misuse    | 93  | 72m | 21f | 60 |
| History of alcohol misuse | 63  | 50m | 13f | 41 |
|                           |     | 63m |     |    |
| Drug plus alcohol misuse  | 45  | 36m | 9f  | 29 |
| Drug or alcohol or both   | 114 | 90m | 24f | 73 |

Table 4

INDIVIDUAL DRUGS USED

| Drugs of misuse                             | M  | F  | Patients (n = 155) |      |
|---|----|----|--------------------|------|
|   |    |    | Total              | %    |
| Cannabis (alone)                            | 20 | 7  | 27                 | 17.4 |
| Cannabis (plus other substances)            | 44 | 10 | 54                 | 34.8 |
| Cannabis (alone, plus cannabis plus others) | 64 | 17 | 81                 | 52.3 |
| Amphetamine                                 | 30 | 5  | 35                 | 22.6 |
| Cocaine                                     | 17 | 7  | 24                 | 15.5 |
| Lysergic acid diethylamide (LSD)            | 17 | 3  | 20                 | 12.9 |
| Ecstasy                                     | 13 | 4  | 17                 | 11.0 |
| Heroin                                      | 9  | 1  | 10                 | 6.4  |
| Crack Cocaine                               | 5  | 1  | 6                  | 3.9  |
| Solvents                                    | 3  | 2  | 5                  | 3.2  |
| Magic mushrooms                             | 4  | 0  | 4                  | 2.6  |
| Barbiturates/Analgesics                     | 2  | 0  | 2                  | 1.3  |
| Heminevrin                                  | 1  | 0  | 1                  | 0.6  |
| Amyl Nitrate                                | 1  | 0  | 1                  | 0.6  |
| Temazepam                                   | 1  | 0  | 1                  | 0.6  |
| Poly drug use (unspecified)                 | 14 | 6  | 20                 | 12.9 |



**Memorandum by Mary Brett BSc, Teacher of Biology and Head of Health Education, Dr Challoner's Grammar School (Boys), Amersham**

**1. PSYCHOLOGICAL EFFECTS OF CANNABIS**

Cannabis is an intoxicant: THC (tetrahydrocannabinol) is the psychoactive constituent.

**1.1 Immediate**

1. Mild euphoria; increased sociability may be followed by a period of anxiety or lowered mood.
2. Very poor social judgement, regression to infantile state, hyperactivity, aggressiveness and agitation were common in some users.
3. Acute psychotic episodes can be triggered in people diagnosed as schizophrenics.
4. An increase in aggressive behaviour of inner-city males has been seen after smoking marijuana.
5. Panic, paranoia, fear of dying, loss of time sense, anxiety, tension and confusion can follow consumption of higher doses. Significant depersonalisation reaches a maximum 30 minutes after smoking.

**1.2 Long Term**

1. Use of cannabis can result in diminished drive, apathy, shortened attention span, distractibility, poor judgement, loss of effectiveness and progressive loss of insight.
2. An increased risk of suicide among heavy users has been reported from Sweden.
3. Marijuana smoking may be a risk factor for schizophrenia.
4. In some respects the effects of cannabis use can mirror the onset of senility and old age.
5. 77,000 people in the USA are admitted annually to treatment programmes for marijuana use and 8,000 require emergency hospital care.

**2. SHORT TERM PHYSIOLOGICAL EFFECTS OF CANNABIS**

**2.1 Immediate**

1. Relaxation, increased appetite and heightened sensory perception.
2. Poor attention span, concentration; passivity and indifference; slow slurred speech.
3. Memory is affected. All capabilities of learning, associative processes and psychomotor performance are impaired including writing, motor co-ordination, divided attention and various operational tasks.
4. A rise in blood pressure occurs and the heart rate rises to over twice the resting rate—similar to that produced by vigorous exercise.

**2.2 Effects on driving ability**

5. There is consistent evidence that there is an increasing risk of motor vehicle accidents if drivers are intoxicated with cannabis.
6. In a 1985 study 36.8 per cent of fatally injured drivers in California had used cannabis.
7. Although nine to 10 times as many people use alcohol, cannabis is detected in a similar number of accidents.
8. Even 24 hours after a 'joint', airline pilots on flight simulators experienced difficulties in landing although unaware of any problems.  
[Car drivers may be considered still unsafe the day after smoking cannabis]

**3. LONG TERM PHYSIOLOGICAL EFFECTS OF CANNABIS**

**3.1 Effects on the Reproductive System and Children**

1. Marijuana lowers testosterone levels in males and disrupts hormone cycles in females.
2. Babies born to marijuana-smoking mothers have lower birth weight and smaller head circumference. Low birth weight correlates with increased risk of ischaemic heart disease later in life; small head circumference correlates with lower intelligence.
3. Long term effects on children include lower scores in verbal and memory tests at 48 months and negative effects on measure of intelligence in three year olds.
4. The incidence of one form of leukaemia among these children showed a 10-fold increase.

5. A comparison of the sperm of hashish users and non-users revealed a significant decrease in sperm count and motility in the users along with distinct structural abnormalities.

### 3.3 *Long Term Effects on the Respiratory System*

1. Chronic bronchitis and emphysema have been reported in regular marijuana smokers.
2. Marijuana smoke contains about 50 per cent more benzpyrene and 80 per cent more benzanthracene than tobacco smoke—both have strong carcinogenic properties.
3. Microscopic examination of bronchial biopsies of heavy hashish users aged 20-26 revealed histopathological changes similar to those found in much older tobacco smokers and known to be precursors of lung cancer.
4. A young man of 27 years died of lung cancer in 1989 after smoking cannabis since the age of 11.
5. Previously rare head and neck cancers characteristic of older tobacco smokers (of average age 64) have become more common in younger cannabis users.
6. Passive inhalation of marijuana smoke has produced sedation in children.
7. Daily marijuana smokers have a 19 per cent increased risk of requiring out-patient visits for respiratory illnesses, a 32 per cent increased risk for injury and a 99 per cent increased risk for other illnesses compared with non-smokers; also a 50 per cent increased risk of admission to hospital.

### 3.5 *Effects on the Immune System*

1. THC inhibits the synthesis of DNA (chromosome material in nuclei of all cells) so new cells made in the body may be adversely affected.
2. Studies have shown that marijuana impairs the production of white blood cells—the body's defence cells.
3. The THC in marijuana damages the immune system such that the user is more susceptible to common viral infections eg colds and influenza and the severity of any infection is likely to be increased.
4. Decreased resistance to infection by *Listeria monocytogenes* and *Herpes simplex* viruses has been demonstrated in cannabis-treated mice. Other drugs which suppress immune responses in mice are generally found to do so in humans.
5. An inability to fight the herpes infections and suppression of a response to treatment of genital warts have been associated with use of cannabis.
6. A 1993 study reported increased numbers of outpatient visits to healthcare centres for respiratory and other illnesses and accidents by marijuana users.

### 3.7 *Long Term Effects on the Nervous System*

1. Memory is affected for weeks after cessation of heavy marijuana use and this interferes with the learning process. Difficulties in complex brain functions may persist for six months.
2. Abnormal changes in brain cells, brain blood flow and brain wave patterns have been documented.
3. Serious and permanent brain damage has been found in monkeys made to smoke the equivalent of 1.5 joints per day for six months.

Cannabis users in the UK give evidence of serious and permanent memory problems. Brain cells, if destroyed, can never be replaced: this gives grave cause for concern.

4. THC (delta-9-tetrahydrocannabinol), one of over 60 cannabinoids detected in cannabis, is most responsible for the 'high' experienced by users. It is readily soluble in lipids (fatty substances) and so quickly dissolves in the lipid-rich membranes of cells. As more THC enters the blood more accumulates in the membranes of brain cells where it may remain, only gradually diminishing, for many days: 40-50 per cent will still be present after 4-8 days, 10-20 per cent after 30 days and traces, detectable in hair and urine, for several weeks.

Brain cells appear to lose their ability to function because the channels through the cell membranes which carry substances essential for metabolism become blocked. This slows down all communication between cells. Ability to plan ahead is diminished. Brain wave studies of "occasional" marijuana smokers among college students at UCLA revealed a 40-50 per cent decrease in "brain energy". The longer the brain cells are impaired, the less chance there is for full recovery.

5. The THC content of cannabis used in the 1960s was about 0.5 per cent; now the average is 5 per cent while specially bred varieties (eg "skunk") may have from 9-27 per cent.



#### 4. CANNABIS: ADDICTION, DEPENDENCE AND TOLERANCE

1. Cannabis can lead to both physical and psychological addiction.
2. A cannabis dependence syndrome is characterised by impairment, loss of control in the use of the substance, cognitive and motivational handicaps interfering with occupational performance. Depression and lowered self-esteem is found especially in long-term users. The risk is highest in those with daily dependence. Half of daily users are estimated to become dependent.
3. Withdrawal symptoms have been noted: anxiety, depression, sleep and appetite disturbances, irritability, tremors, sweating, nausea, muscle convulsions and restlessness. However, since the cannabinoids are fat-soluble and released slowly, withdrawal is ameliorated by their continued presence.
4. A study of 200 long-term users of cannabis in Australia (averaging 11 years of use) has shown that 92 per cent were physically dependent, 40 per cent severely dependent, women being more susceptible than men. As with alcohol about 10 per cent of all who have tried cannabis may become dependent. In another study in New Zealand young males (at 21 years) were more likely to be dependent than females.
5. A cannabinoid receptor has been found in the brain, most abundantly in the basal ganglia, cerebellum, cerebral cortex and hippocampus. This distribution would appear to correlate well with the effects of cannabis on the human brain. Withdrawal has been precipitated in animals chronically treated with cannabinoids by treatment with a "receptor antagonist".
6. An endogenous substance in the brain (the ligand anandamide) possesses similar pharmacological properties to delta-9-THC although less potent and has a shorter duration of action. The endogenous receptor is presumably normally associated with this natural brain substance. There is also evidence that anandamide acts as a neurotransmitter and is perhaps one of a family of such substances.
7. Tolerance to most of the effects of THC has been demonstrated in both animals and humans. Degree of tolerance is similar to that produced by some opiates and many characteristics of THC tolerance are similar to those of the opiates, nicotine and alcohol.
8. Tolerance involves increased drug dosage to achieve the desired effect. Where formerly cannabis with THC content of 0.1 per cent produced a "high", today's marijuana with THC at 6–14 per cent will cause experienced users to "mellow out" rather than become "high". Brain cells become adapted to THC and so are not acutely activated by the presence of such large amounts.
9. The pure prescription form of THC, Marinol, carries a warning "Marinol is highly abusable and can produce both physical and psychological dependence. Patients receiving it should be closely observed."
10. There have been over 77,000 admissions annually to treatment programmes in the US for marijuana abuse and 8,000 have needed admission to hospital.
11. Two recent studies have shown that there are similarities between the effects of marijuana on the brain and those produced by the highly addictive opiates, alcohol, nicotine and cocaine. Withdrawal from all these drugs causes release of the corticotropin releasing factor (CRF) which results in symptoms of anxiety and stress. THC has been found to produce a "dopamine rush" (dopamine is a neurotransmitter) which is part of the "reward system" that ensures the user will come back for more. This biochemical event is also triggered with alcohol, nicotine, opiates and cocaine. THC has also been found to affect opiate receptors in the brain.

#### 5. CANNABIS AS A MEDICINE

##### 5.1 *Introduction*

Marijuana contains 66 cannabinoids and over 300 other identified chemical components; when burnt, over 2,000 chemical substances are produced. Pure delta-9-THC (tetrahydrocannabinol), the psychoactive cannabinoid, is available to physicians in synthetic form under the names Nabilone (in the UK) and Dronabinol or Marinol (in USA) and it may be prescribed to relieve nausea caused by chemotherapy in cancer treatment and as an appetite stimulant for AIDS patients. Most of the research into the medical use of cannabis has been done with pure synthetic THC, taken orally or in suppositories, and with crude marijuana either smoked or ingested in herbal preparations. There is no difference in pharmacological effect between THC isolated from cannabis and the synthetic THC as marketed in the USA.

##### 5.2 *Cancer Chemotherapy—Nausea*

1. Sallan et al found negative side effects in 81 per cent of patients given THC orally, 9 per cent of these having hallucinations, distortion of reality and mental depression. The effectiveness usually correlated with onset of the "high" (feeling of intoxication).
2. In one study blood plasma levels of THC as low as 10 ng/ml were found to be effective in preventing nausea. In another study the toxicity of THC appeared so profound that most patients preferred the nausea, even though the level of THC in the plasma (300 ng/ml) was similar to that experienced by marijuana users at intoxication.

3. Nausea was also partially or completely resolved in 72 per cent of cases with a dosage of five mg/m<sup>2</sup> of body surface area. Drowsiness was a very common side effect.

4. Studies with smoking marijuana have generally been self-evaluated and lacking experimental controls but in one random double-blind experiment, in which pure THC and smoked marijuana were compared, 35 per cent of patients reported THC to be the more effective at controlling nausea while 45 per cent found no difference.

5. Oral THC in doses of five to 15 mg/m<sup>2</sup> body surface are effective in treating nausea associated with cancer chemotherapy if patients are treated before vomiting occurs and the doses are repeated every three to six hours for about 24 hours.

6. Many other drugs are safe and effective for this purpose, eg Ondansetron, Prochlorperazine, Lorazepam and Promethazine. The National Cancer Institute recommends that THC should only be used as a last choice if no other treatment is successful but side effects must be weighed against possible benefits to the patient.

7. In 1997 1,500 clinical oncologists in the USA were sent a survey questionnaire related to these treatments to which 75 per cent replied. In the past 12 months, 98 per cent had prescribed or recommended serotonin antagonists (Ondansetron or Granisetron) for nausea, 6 per cent had prescribed Marinol (Dronabinol) and 1 per cent marijuana to be smoked. Although 30 per cent were in favour of re-scheduling marijuana for medical purposes, most estimated that they would write less than one prescription per month for marijuana cigarettes.

### 5.3 *Appetite stimulation in AIDS patients*

1. A double-blind placebo-controlled parallel group study showed that 2.5 mg oral THC twice daily effectively stimulated the appetite of patients with AIDS, ie weight was maintained or increased slightly.

2. Another double-blind placebo-controlled study compared the effects of oral and rectal suppository preparations of THC with those of smoked marijuana in *healthy*, experienced marijuana smokers. Appetite stimulation and weight gain showed no difference between methods of administration.

3. Since THC damages the immune system, which in AIDS patients is already compromised, patients receiving THC would be expected to be more susceptible to colds, influenza and other viral infections, and illnesses already suffered would be rendered more severe.

### 5.4 *Multiple Sclerosis*

Clinical evidence is scant on the effects of THC or crude marijuana on MS patients. However, one randomized double-blind, placebo-controlled study of the effects of marijuana smoking in patients with MS showed posture and balance to be negatively affected and worse than the baseline. This was consistent with the deterioration of mental, motor and postural functions seen in another study with normal, healthy volunteers.

### 5.5 *Glaucoma*

1. Except in rare cases, glaucoma is a symptomless disease until loss of sight begins.

2. Along with other cannabinoids, THC does lower pressure in the eye (intraocular pressure) in laboratory animals and humans with glaucoma.

3. Following an experiment using marijuana it was concluded that, because of the side effects of hypotension, tachycardia, palpitation and altered mental state, use of such drugs in the general population was not appropriate.

4. The drop in intraocular pressure after smoking marijuana in acute studies lasts about four to five hours, the maximum fall occurring at one to two hours after administration. To be effective chronic administration of marijuana would be needed six to eight times daily for the duration of the disease. Dr Keith Green stated that some six "joints" a day would be required, thus rendering the patient effectively "stoned" and incapable of useful activities.

5. There is no evidence that THC or crude marijuana actually affects or arrests the underlying disease.

6. Carl Kupfer, Director of the National Eye Institute (USA), explains that when intraocular eye pressure is reduced by these means so also is blood pressure and this will affect the blood supply to the eye: visual function may therefore still be lost.

7. The American Academy of Ophthalmology, with over 12,000 physicians and 6,000 other medical ophthalmic professionals in its membership has concluded that there are insufficient data to demonstrate the safety and efficacy of using smoked marijuana in the treatment of glaucoma; the National Academy of Sciences has stated that "smoking marijuana is not suitable for the treatment of glaucoma".

8. A Review article by Quigley on the treatment of glaucoma published in the New England Journal of Medicine in 1993 makes no mention of marijuana in its consideration of effective medication for this disorder.



## 6. CONCLUDING POINTS FOR CANNABIS AS A MEDICINE

### 6.1 *Criteria for medicines*

The issue of whether to allow smoking marijuana to be prescribed as medicine was clarified on February 18 1994 in the US Court of Appeals for the District of Columbia. It set new guidelines that only rigorous scientific proof can satisfy the requirement of “currently accepted medical use”. The criteria are as follows:

- i. The drug’s chemistry must be known and be reproducible.
- ii. There must be adequate safety studies.
- iii. There must be adequate and well-controlled studies proving efficacy.
- iv. The drug must be accepted by qualified experts.
- v. The scientific evidence must be widely available.

None of these criteria is currently satisfied in the case of crude marijuana.

### 6.2 *Institute Reports and Views*

#### 6.2.1 US National Institutes

In 1992 the US National Institutes of Health Scientists reported as follows:

- i. The National Eye Institute: The intraocular pressure lowering action of marijuana is not effective enough to prevent optic nerve damage in glaucoma and “there is no scientifically verifiable evidence that marijuana or its derivatives are safe and effective in the treatment of glaucoma”.
- ii. The National Cancer Institute: Newer anti-emetic agents such as ondansetron have been shown to be more useful than THC as a first line therapy.
- iii. The National Institute of Dental Research. There have been no controlled studies which substantiate claims for marijuana’s anti-pain effects.
- iv. The National Institute of Allergy and Infectious Disease: The many carcinogens in marijuana smoke would be a concern especially for patients with compromised immune systems. Studies of pure THC in oral and suppository form are being conducted in patients with AIDS wasting syndrome.
- v. In conclusion the Report determined that there are better and safer drugs than crude marijuana for all conditions considered.

#### 6.2.2 International View on Use for MS

In respect of MS, the American, British and International Institutes are currently against the use of marijuana. Dr Donal Silberg, Chief of Neurology at the Pennsylvania School of Medicine, has said “I have not found any legitimate medical or scientific works which show that marijuana is medically effective in treating multiple sclerosis or spasticity. The use of marijuana especially for long-term treatment would be worse than the illness itself”.

#### 6.2.3 BMA Report

The BMA, in their Report entitled “The Therapeutic Uses of Cannabis” (November 1997), concluded that cannabis itself is unsuitable for medical use, but that certain additional cannabinoids should be legalised for wider medical use.

#### 6.2.4 Proposition 200

In Proposition 200 (November 1996) physicians in California were permitted to recommend, and in Arizona to prescribe, crude marijuana with no limitations on the age of the patient or disorder involved. A public opinion poll in January 1997 conducted by Dr Bruce D. Merrill, Professor of Mass Communications and Director of Media Research Centre, Walter Cronkite School, Arizona State University, revealed that 85 per cent of registered voters believed Proposition 200 should be changed and 60 per cent wanted it repealed.

#### 6.2.5 Dr Eric Voth—Personal View

Dr Eric Voth, Chairman of the International Drug Strategy Institute, said in a letter to the Editor of the New England Journal of Medicine (27 January 1997)

“Long-term effects aside, contaminants, purity, standardisation of dose etc, are all reasons to not use an impure herb as a medicine.

Whether terminal or not, should we support smoking foxglove plant to obtain digoxin for heart failure, or yew tree bark to obtain taxol for breast cancer? If so, then supporters of smoked marijuana better be ready to support smoking tobacco for weight control and anxiety.

We must have compassion for the sick and suffering, and we must offer them reliable and quality medicine, not crude substances that threaten their well-being".

#### 6.2.6 Concluding Remarks

In conclusion it would appear that all scientific evidence is unequivocal in favour of maintaining prohibition of crude marijuana for both medical and recreational use. However, purified cannabinoids may, after rigorous testing and clinical trials in comparison with other and existing treatments, prove to be beneficial in certain disorders as is the case with nabilone and dronabinol.

4 May 1998

#### Supplementary Letters from the British Medical Association

Thank you for your letter of 7 May 1998 concerning the Home Office response to the BMA's evidence to the Select Committee (*see Home Office letter, p149*).

The statistics on Home Office research licences for cannabis referred to in the BMA evidence were obtained from an All Party Parliamentary meeting held at the House of Commons in December 1997 at which representatives from the BMA were present. The BMA would like to take this opportunity to thank the Home Office for clarifying the situation regarding the research licensing scheme for cannabis. We are very pleased to hear that applications are dealt with as expeditiously as circumstances allow and that there are no applications outstanding.

We thank you for drawing this to our attention. I shall send a copy of this letter to Mr MacFarlane at the Home Office.

20 May 1998

Further to your recent telephone conversation with Professor Ashton today, I understand that you seek clarification on two points raised in our report *Therapeutic Uses of Cannabis*.

On page 39, we state that depending on the results of clinical trials there may be a case for considering the extension of indications for nabilone for use on a named patient basis, in chronic spastic disorders which are unresponsive to standard drugs. On page 80, we state that carefully controlled trials in the medical use of cannabinoids should be a priority for patients with chronic spastic disorders, but in the meantime, there is a case for the extension of the indications for using nabilone and THC in chronic spastic disorders.

We would like to take this opportunity to clarify the BMA policy on this issue, that consideration should be given for the extension of the indications for nabilone and THC for use in chronic spastic disorders for patients who are unresponsive to standard drugs at present, but that research and carefully controlled trials should continue to be a high priority.

I hope that you find this acceptable and apologise for the apparent inconsistency.

Professor Vivienne Nathanson

Head Professional Resources and Research Group

12 June 1998

#### Memorandum by the Christian Institute

#### HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF PERMITTING MEDICAL USE?

##### INTRODUCTION

1. The debate in this area tends to focus around calling on the Government to take the following steps:

- To reschedule cannabis from schedule 1 to schedule 2 of the Misuse of Drugs Act
- To permit certain sufferers to use cannabis whilst research is underway

2. We agree with the recent BMA report which concludes that "cannabis is unsuitable for medical use"<sup>8</sup>. We argue that the scientific support for its medical use is wholly inadequate. There are many anecdotal claims that cannabis provides relief from certain kinds of suffering, but a recommendation either to reschedule or to grant legal exemption for medical use cannot be justified on the basis of science.

<sup>8</sup> BMA *Therapeutic uses of cannabis*, BMA/Harwood Academic Publishers, 1997, pages 68–69.



## CANNABIS AND CANNABINOIDS

3. There is a crucial distinction to be made between cannabis and cannabinoids. The BMA report calls for the focus of future research to be on cannabinoids rather than cannabis: “The information is meagre but nevertheless it can be concluded that although cannabis itself is unsuitable for medical use, individual cannabinoids have a therapeutic potential in a number of medical conditions in which present drugs or treatments are not fully adequate”<sup>9</sup>.

4. Professor Wall has criticised the BMA report for focusing on cannabinoids rather than herbal cannabis which may have synergistic effects. It is perfectly true that in clinical practice some drugs are used “synergistically” in combination with other drugs. Sometimes the mechanism of action is not known, but the effect of the combination of drugs can be studied and replicated because each drug is of a known concentration.

5. To prescribe a plant is to bend the fundamental rules of medicine. Doctors do not prescribe a cocktail of drugs of unknown strength. Yet this is precisely the effect of prescribing herbal cannabis. The BMA report puts it well: “cannabis contains over 400 chemical compounds including more than 60 cannabinoids. Furthermore, there is considerable variation in the concentration of cannabinoids present in different preparations. Even if cannabis (either smoked or taken orally) from standardised preparations were shown to have therapeutic benefits, it would not be possible to know which particular agents (or combination of agents) were beneficial, and medical knowledge would not be advanced or treatment improved. For these reasons, as well as the known toxic constituents in cannabis smoke mentioned above, it is considered here that cannabis is unsuitable for medical use. Such use should be confined to known dosages of pure or synthetic cannabinoids, given singly or sometimes in combination (eg THC and cannabidiol)”<sup>10</sup>.

6. In the very nature of things it is difficult to carry out scientific research on the medical effects of a plant. The BMA report also goes on to deal with the problems of purity of street and illicit cannabis and naturally occurring contaminants such as microbes and fungi. All these factors mean that future research should focus on cannabinoids.

## SHORT-CIRCUITING THE SCIENTIFIC PROCEDURES

7. It is scientific evidence that must determine which substances are rescheduled to schedule 2 of the Misuse of Drugs Act. And the rules must remain the same for all substances. As Paul Boateng, the Health Minister, has said to Austin Mitchell: “We should not accept a lesser standard of evidence in the case of cannabis because of the pressures, to which my honourable friend has contributed—properly, as he sees it—on behalf of people who are convinced of its therapeutic value.”<sup>11</sup>

8. Anecdotal evidence, no matter how moving, is not scientific research. Rescheduling cannabis would declare that cannabis is suitable for medical use. The studies have not been done to demonstrate this.

9. Professor Ashton has shown most of the studies on cannabis were carried out in the 1970s using a much lower potency of THC than is used today. A typical 1970s “reefer” contained about 10mg of THC, while today a joint may contain 60–150mg of THC. Many of the studies involved small numbers of patients and were not double blind and placebo controlled<sup>12</sup>.

10. The Government is right to argue that “Much of the existing research evidence on the use of cannabis is flawed, and is recognised as such.”<sup>13</sup>

11. The strongest studies are those which show the anti-emetic properties of THC in patients on chemotherapy for treatment of cancer. This has led to nabilone and dronabinol being licensed for use in the UK. We accept that further research is needed. If other cannabinoids can be shown after clinical trials to have a proper medical use then we can see no obstacle to them being licensed.

12. Austin Mitchell MP, has claimed that “In effect, there has been a total block on research” since 1971 when cannabis was put on schedule 1.<sup>14</sup> But Paul Boateng, the Health Minister, has stated that a total of 22 licences have been given for research on cannabis, of which 19 are still current. Three are concerned directly with medical research involving patients and no applications have been rejected in the recent past.<sup>15</sup>

13. The BMA states that the evidence for the therapeutic potential of cannabinoids is “meagre”. This is the primary reason as to why there are difficulties in carrying out research: drug companies are understandably reluctant to fund work on such a slender evidence base. Even the established uses of cannabinoids are undertaken only when other treatments have failed.

<sup>9</sup> *Ibid*, page 77.

<sup>10</sup> *Ibid* pages 68–69.

<sup>11</sup> House of Commons: Hansard 14 January 1998 col 320.

<sup>12</sup> See *BMA Therapeutic uses of cannabis*, *Op cit*, Appendix III, pages 102–117.

<sup>13</sup> House of Commons: Hansard 14 January 1998 col 321.

<sup>14</sup> *Ibid* col 317.

<sup>15</sup> *Ibid* col 322.

14. The Government is discussing with the BMA how further research on cannabinoids can be encouraged. Meanwhile it would set a very bad precedent indeed to short-circuit the scientific evidence and permit doctors to prescribe cannabinoids for indications for which there is no soundly based research. Such a step would have much wider implications.

15. To permit MS sufferers, for example, to grow and smoke their own cannabis as the Alliance for Cannabis Therapeutics (ACT) are advocating would profoundly damage current health promotion attempts to dissuade smoking. Even if it were possible for MS sufferers to make their own preparations of cannabis to be taken without smoking, the dosage would not be controlled and there would also be psychoactive effects. According to Professor Ashton, the dosages described by Clare Hodges of ACT, are enough to cause intoxication (2.5 mg–5 mg of THC).

#### MULTIPLE SCLEROSIS

16. The fact that some MS sufferers are breaking the law by smoking cannabis indicates a level of dissatisfaction with the present treatments. Some effective drugs used in the treatment of MS are very expensive. This limits their availability.

17. Whatever politicians may say, decisions about the rationing of health care are taken all the time. There does need to be a more open and democratic debate in this area. It may well be that MS as a disease has not fared particularly well as decisions about the allocation of resources have been taken.

18. The evidence regarding the therapeutic use of cannabinoids may be meagre, but following the discovery of cannabinoid receptors it should be possible to develop selective cannabinoid agonists and antagonists for use as a therapeutic agent.<sup>16</sup> It seems realistic to expect the development of cannabinoid drugs that bind only to CB2 receptors (away from the brain). The committee should therefore call for greater research funding in this area.

#### IS "MEDICAL MARIJUANA" A FRONT FOR LEGISLATION?

19. This is a question that has been asked by the Committee during its public hearings. We have no doubt that there are sincere people advocating cannabis use for medical purposes whose only concern is to alleviate suffering. We also have no doubt that the efforts of these sincere people are being cynically deployed by other groups seeking legalisation. These groups are well aware of the propaganda value of gaining ground in the "medical marijuana" debate.

20. NORML (National Organization for the Reform of the Marijuana Laws), one of the largest legalisation groups in America, petitioned the Drugs Enforcement Agency (DEA) for the re-scheduling of marijuana (cannabis) in 1972. In 1979 the founder of NORML was quoted in the University of Emory Magazine: "We are trying to get marijuana reclassified medically. If we do that, . . . [we will] . . . be using the issue as a red herring to give marijuana a good name."<sup>17</sup>

21. In 1989 the DEA denied the petition and published a lengthy critique of the evidence presented<sup>18</sup>. Various legal actions against the administration ensued. In 1994 the US Assistant Secretary of Health commissioned a comprehensive review on the medical use of cannabis. This concluded "There is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis or intractable pain."<sup>19</sup>

The US Court of Appeals accepted the Government's ruling that marijuana did not have an accepted medical use.

22. In 1996 two US states held plebiscites on whether marijuana should be available for medical use. The American billionaire, George Soros, has admitted to giving \$1 million to fund the successful campaigns in California and Arizona. Other businessmen also followed suit. Mr Soros also funds the Lindesmith Centre in New York, an organisation which was well represented at the *Independent on Sunday* Conference held at the Queen Elizabeth Conference Centre on the legalisation of cannabis in the autumn of last year. This conference was sponsored by the Body Shop and Richard Branson.

23. President Clinton's administration along with former Presidents Bush, Ford and Carter all campaigned against the propositions which were passed by 54 per cent to 46 per cent in California and by 65 per cent to 35 per cent in Arizona. Immediately after the motions were passed there was a conflict with Federal Law which prohibits the purchase of marijuana. US Attorney Janet Reno wrote to every doctor in California and Arizona warning them that if they prescribed marijuana they could lose their license to practice and face prosecution.

<sup>16</sup> See BMA *Therapeutic uses of cannabis*, *Op cit*, page 17.

<sup>17</sup> Quoted in Maginnis R. *America Assesses 'Medical' Marijuana*, Family Research Council, 1997, page 4.

<sup>18</sup> *Marijuana rescheduling petition denied by DEA*, The Federal Register, Vol 54, No 249, Dec 29, 1989.

<sup>19</sup> Quoted in *Drugs Bulletin* 1997–98, The Christian Institute, page 37.



24. The DEA argued that the terms of the Arizonan motion were so wide that heroin and LSD could also be prescribed by doctors. In April the Governor of Arizona signed a Bill into law which effectively overturned the legislation which followed from the proposition. This new legislation requires that the drugs prescribed by doctors must also be approved by the Federal Drugs Administration (FDA). The FDA have not approved any controlled substance.<sup>20</sup>

25. One of the main ways in which cannabis legalisation campaigners disseminate information is over the internet. UK Cannabis Internet Activists (UKCIA) have a site on the world wide web, a section of which is devoted to campaigning for medical cannabis.<sup>21</sup> Cannabis can also be purchased over the internet.

26. In the light of the fact that legalisation campaigners are keen to use the medical cannabis argument, we believe that it would be very helpful if the Select Committee explicitly states that it supports the present illegal status of cannabis. Certainly new scientific evidence has strengthened the case for the status quo.

### *How strong is the scientific evidence in favour of maintaining prohibition of recreational use?*

#### THE CHANGING SCIENCE

27. Professor Ashton in her evidence to the Committee states that the present day cannabis "joint" has been six and 15 times the THC content of a 1970s "reefer".<sup>22</sup> She writes "most of the research on cannabis was carried out in the 1970s using relatively small doses, and much of that research is obsolete today. The acute and long-term effects of the present high dose use of cannabis have not been systematically studied".<sup>23</sup>

28. New evidence on dependence and addiction was reported last year. This seems to demonstrate marked similarities between the way cannabis affects the brain and the effect produced by drugs such as cocaine and heroin.

29. Tanda et al have shown<sup>24</sup> that THC activates the same reward areas of the brain (the nucleus accumbens) and releases the same chemical (dopamine). Addictive drugs probably cause compulsive behaviour by unleashing a dopamine surge of their own. Tanda has been the first to demonstrate that cannabis induces the dopamine rush. They found the magnitude of the surge in the nucleus accumbens of rats infused with THC was similar to that of the surge in rats infused with heroin.

30. Di Chiara, a co-author of the Tanda study, in an interview with *Science* said "I would be satisfied if, following all this evidence, people would no longer consider THC a 'soft drug'. I'm not saying it's as dangerous as heroin, but I'm hoping people will approach marijuana far more cautiously than they have before."<sup>25</sup>

31. Another study by de Fonseca et al considered the symptoms of stress caused by marijuana withdrawal to a peptide in the brain called corticotrophin-releasing factor (CRF).<sup>26</sup> This same chemical has already been implicated in the anxiety and stress experienced during opiate, alcohol and cocaine withdrawal. Levels of CRF in a structure known as the amygdala directly correspond to the anxiety and stress levels of the rats during withdrawal. These results provide the first neurochemical basis for a marijuana withdrawal syndrome. Weiss, a member of de Fonseca team, suggests that a desire to avoid anxiety and other negative emotions associated with withdrawal may prompt a vicious cycle leading to dependence.<sup>27</sup>

32. The Parliamentary Office of Science and Technology in their April 1998 briefing on cannabis comment: "From one view recent findings are tending to confirm the risks previously dismissed as theoretical by some".<sup>28</sup> "the discovery that cannabis may act on chemical pathways involved in dependency and withdrawal is also leading to calls for the dependency potential of cannabis to be re-evaluated (upwards)".<sup>29</sup>

33. The World Health Organisation also produced a substantial report on Cannabis in 1997. This drew attention to the developments in research: "There have been significant advances in research of the last 15 years . . . There has also been substantial progress in understanding the chronic effects of cannabis on the respiratory system and on various types of cells in the body's immune system. Chronically, there are selective impairments of cognitive functioning and dependence syndrome may develop. Chronic cannabis use may also exacerbate schizophrenia in affected individuals".<sup>30</sup>

<sup>20</sup> *Ibid*, page 36.

<sup>21</sup> <http://www.foobar.co.uk/users/ukcia/medical/index.html>.

<sup>22</sup> Ashton C H *Cannabis, Evidence submitted to the House of Lords Select Committee on Cannabis*, April 1998, para 1.1.

<sup>23</sup> *Ibid*, para 1.2.

<sup>24</sup> Tanda G, Pontieri F E and Di Chiara G *Cannabinoid and Heroin Activation of Mesolimbic Dopamine Transmission by a Common  $\mu_1$  Opioid Receptor Mechanism*, *Science* 1997; 276: 2048–2050.

<sup>25</sup> *Science* 1997; 276: 1968.

<sup>26</sup> de Fonseca F R, Carrera M R A, Navarro M, Koob G F and Weiss F *Activation of Corticotrophin-Releasing Factor in the Limbic System during Cannabinoid Withdrawal*, *Science* 1997; 276: 2050–2054.

<sup>27</sup> *Science* 1997; 276: 1967.

<sup>28</sup> Parliamentary Office of Science and Technology (POST) Note 113 March 1998, page 4.

<sup>29</sup> *Loc cit*.

<sup>30</sup> *Cannabis: a health perspective and research agenda*, Division of Mental Health and Prevention of Substance Abuse, World Health Organisation, 1997, page ii.

34. We would submit that the new scientific evidence is showing that cannabis is not as soft a drug as has been thought. The concepts of dependence and addiction once dismissed as impossible with cannabis are now commonly discussed in the scientific literature.

#### SCIENTIFIC KNOWLEDGE AND THE GOVERNMENT'S DRUGS STRATEGY

35. The Government's White Paper on Drugs states that "All activity supported by this strategy will: inform young people, parents, and those who advise/work with them about the risks and consequents of drug misuse . . . ." <sup>31</sup>

This is the first objective of the first aim. Clearly providing young people with accurate information about drugs is at the heart of the Government's strategy.

36. Scientific knowledge by its very nature develops over time. But changes in knowledge take time to filter through the various levels of our education system and to the advice leaflets given to young people. When it comes to drugs we would estimate that there is a time lag of two or three years before developments in science are turned into materials which teach young people about drugs.

37. This was the case with ecstasy. Before the death of Leah Betts, it was confidently asserted that no one has died from taking ecstasy. The advice materials published before her death were still being distributed after her death.

38. The idea that cannabis is a "gateway drug" leading to harder drugs, now has robust scientific support following recent studies. But the Health Education Authority's new world wide web site, launched in 1998 to give drugs information to young people states: "Some people believe that cannabis is a "gateway" drug and think that cannabis users are more likely to go on to use harder drugs such as heroin. There is no evidence to support this belief." <sup>32</sup>

This is simply untrue.

39. We believe that it is right for young people to have accurate information about the effects of drugs on the body. It is in everyone's interest for scientific knowledge to be made widely known. However we have two concerns. Firstly as the Government implements its strategy it is vitally important that the scientific base which underpins drugs education is truly accurate and up to date. Secondly it has to be recognised that with young people there will always be limitations on how they can assess the scientific information presented to them.

#### WHOSE HEALTH?

40. In considering the health implications of cannabis it is impossible to ignore the wider health consequences for families and for society as a whole.

41. There have not been systematic studies involving the present high dose use of cannabis. Society often decides that the freedom of individuals must be limited in order to protect innocent victims. The health of innocent victims is certainly effected by cannabis.

42. It is known that exposure *in utero* has been linked to leukaemia, lower birthweight and smaller head circumferences in babies and negative effects on measures of intelligence in three year olds. <sup>33</sup>

43. The DETR study on fatally injured drivers in 1997 estimated that 37 drivers per month tested positive for illicit drugs. Cannabis makes up 21 of these compared with seven in the 1985-87 study. Whilst the figures for cannabis have risen three-fold in just over 10 years, the figures for alcohol have significantly fallen from 46 fatally injured drivers per month in 1985-87 to 27 drivers per month in 1997. <sup>34</sup>

44. These are the figures for fatally injured drivers who test positive for cannabis. There are also innocent victims in other cars or on the pavements, one of whom was related to an author of this submission.

45. Professor Heather Ashton has carried out a comprehensive review of the scientific evidence for the Department of Health in March 1996. In her view, and in the view of the Government, this constitutes strong scientific evidence in favour of maintaining prohibition of the recreational use of cannabis. <sup>35</sup> We strongly concur with this view.

*Alison Back BSc*  
Medical Researcher

*Colin Hart BSc PGCE*  
Director

11 May 1998

<sup>31</sup> *Tackling Drugs*, Cm 3945, The Stationery Office Ltd, page 15.

<sup>32</sup> Health Education Authority, world wide web site on drugs (<http://www.trashed.co.uk/newframe.cgi?714>).

<sup>33</sup> See *Drugs Bulletin*, *Op cit*, page 15.

<sup>34</sup> DETR, (Press Notice 149/Transport), 27 June 1997.

<sup>35</sup> Ashton C H *Op cit*, para 11.1.



## Memorandum by David Copestake

### 1. INTRODUCTION

1.1 I am told by a friend who is a research chemist that a natural substance such as a plant product is far more useful for making drugs than a synthetic compound. Cannabis contains over 400 chemicals and so may possibly be of use in providing drugs of medicinal value. The active constituents or cannabinoids have numerous properties including psychotropic effects, bronchodilation, increased heart rate, reduced intraocular pressure, analgesia, alterations of body temperature, anticonvulsant activity and so forth.

1.2 No doubt because of these varied effects, cannabis has been used in folk medicine in the East for thousands of years. It is reported that a Chinese Emperor of about 3,000 BC recommended hemp products to treat female weakness, gout, rheumatism, malaria, beriberi, constipation and absentmindedness (D B Louria, "The Drug Scene", London, 1970, p.104.) In India, ganja and bhang have been prescribed for a whole variety of complaints especially gastro-intestinal complaints and catarrhs, as a nervous stimulant, and as a source of great staying power in cases of severe exhaustion or fatigue. Some years ago in Britain, cannabis extracts were used as a medicine, but were then discontinued. In recent years with the growth of the pot culture, extravagant claims are again being made for cannabis as a medicine.

1.3 The World Health Organisation has repeatedly stated that cannabis preparations are obsolete and that the dangers involved would outweigh possible therapeutic advantages. Scientific research has been, and is being carried out on cannabis as a therapeutic agent such as in the treatment of asthma and glaucoma. A search is being made to separate the psychoactive properties from the analgesic (prevention of pain) properties of cannabinoids. Research has been done on the prevention of nausea in the treatment of cancer by chemotherapy, and the drug Nabilone (or similar) has been produced for this treatment. This is a synthetic cannabinoid.

1.4 Emotional appeals are now being made to the public claiming that cannabis is a valuable medicine for all sorts of illnesses, and that people should be legally able to smoke it.

### 2. MEDICAL OPINION ON CANNABIS

2.1 Let us look at what scientifically informed opinion says about cannabis as a medicine.

2.2 Cannabis was deleted from the British pharmacopoeia in 1932 because of its variability and unreliability. It has a large number of harmful side effects: it is more carcinogenic than tobacco; it damages the immune system; it harms the brain and neural systems; it damages the foetus when taken during pregnancy; it causes respiratory complications and problems; it causes abnormalities in the cells lining the airways of the upper and lower respiratory tract and in the airspaces deep within the lungs. Cannabis smoke is also known to include certain forms of bacteria and fungi and those at most risk from these are those with impaired immunity such as Aids patients and cancer chemotherapy patients. Cannabis is addictive too with a physical dependence and psychological habituation, but the cannabis addict is exceptionally slow to recognise the addiction.

2.3 These factors show that the drug bears a substantial health risk and for chronic use with patients at high risk of infection, the risks are unacceptable.

### 3. CLAIMED OR POSSIBLE MEDICAL USES

#### 3.1 *Glaucoma*

The pro-drug forces assert that millions of glaucoma sufferers must have access to the alleged miracle drug cannabis. However with cannabis, the psychoactive effect remains requiring the glaucoma sufferer to maintain a psychotropic high in order to keep the intraocular pressure reduced. Alcohol also produces a profound reduction in aqueous humor formation and intraocular pressure in the eye. The recommendation to use cannabis is exactly like suggesting the patient maintain a state of drunkenness to treat glaucoma. There are other and better treatments available for glaucoma and it is unfortunate to see glaucoma used as a political tool to advocate legalization of a recreational drug. Cannabis offers no advantage over other drugs.

#### 3.2 *Multiple Sclerosis*

3.2.1 MS is a central nervous system disease that is always unpredictable and often crippling. There is no evidence that cannabis is effective in modifying the course of MS. There have only been anecdotal reports of benefit of some of the symptoms associated with MS—spasm and pain—after the use of cannabis.

3.2.2 A double-blind, randomized, placebo-controlled study of inhaled marijuana smoke in ten adult patients with spastic MS demonstrated that marijuana smoking impairs co-ordination and balance in patients with spastic MS. (Greenburg *et al* in *Clinical Pharmacology and Therapeutics*, Vol 55: 324-328, 1994, cited in *Marijuana Research Review*, Vol 2, No 1, Jan 1995.)

### 3.3 *Nausea in chemotherapy*

3.3.1 The problem again is that the negative effects of cannabis far exceeds those for most of the other agents available. The pro-drug lobby would have us believe that millions of cancer sufferers are going untreated, but this is not the case. There is some evidence that cannabis is effective in treating nausea associated with chemotherapy, but efficacy is often associated with a sensation of intoxication. Again it is similar to having a patient drunk all day to control the symptoms. The synthetic cannabinoid Marinol is not advised as a first line drug, but for use only in patients who have failed to respond to other treatments. They are also told to remain under supervision during use.

3.3.2 A study of eight children aged 3 to thirteen years in Israel using delta-8-THC showed great success in preventing vomiting and the side effects observed were negligible. No anxiety or hallucinogenic effects were noted in spite of the high doses administered. Delta-8-THC is a cannabinoid with lower psychotropic potency than the main cannabis constituent, delta-9-THC (Dronabinol). The authors of this study believe this cannabinoid can serve as a new, inexpensive antiemetic agent in pediatric cancer chemotherapy. (A. Abrahamov, A. Abrahamov and R. Mechoulam, "An efficient new cannabinoid antiemetic in pediatric oncology", *Life Sciences*, Vol 56, Nos 23/24, pp 2097–2102, 1995.)

### 3.4 *Pain*

There is insufficient evidence to recommend cannabis as the treatment of choice for any patient with any pain condition. For most patients the drug will have problematic side effects. There may be some patients for whom cannabis is a moderately effective pain reliever when no other treatment is of benefit, but this has not been rigorously studied. (Department of Health and Human Services, Washington DC.)

### 3.5 *Asthma*

Smoked cannabis, and to a lesser extent oral THC, have a mild bronchodilatory effect in both normal persons and persons with asthma. However this effect is outweighed by the fact it produces bronchial irritation, reduced antibacterial activity in the lung, and gives a possible risk of cancer. The unwanted psychotropic effects have also been a barrier to its use as an anti-asthmatic drug, and some subjects get uncomfortable heart effects (tachycardia) through the drug.

### 3.6 *Sleep*

Cannabis does promote sleep, but there is a hangover, and also some people do not like the unreal feeling it gives. THC also suppresses REM (Rapid Eye Movement) sleep, and so it is likely that the patient's disturbances are themselves caused by the cannabis use.

### 3.7 *Depression*

Some people smoke cannabis as a self-medication for depression, and often cite depression as a reason for their use of the drug. However, they do not realise that depression is a common consequence of cannabis use. Cannabis users will continue to use the drug in spite of worsening depression.

### 3.8 *Epilepsy*

Some constituents of cannabis promote fits, while others are anti-epileptic. The cannabinoid Cannabidiol (CBD) shows some anticonvulsant action. It is said that because it is chemically unrelated to other anticonvulsants, it could offer an alternative for those in whom other drug therapies fail to control seizures. There have been few studies of this, partly because CBD is difficult to prepare, and the results so far are inconclusive.

### 3.9 *Appetite stimulant for AIDS patients*

The synthetic cannabinoid Dronabinol has been approved by the US Food and Drug Administration as a food intake stimulant for AIDS patients suffering from wasting syndrome. This was based on a study by Plasse *et al* in 1991. However, because of the immunosuppressive effects of cannabinoids, even a small further impairment of immunity, may have major consequences for HIV and AIDS affected individuals.

## 4. FURTHER RESEARCH

4.1 As mentioned earlier, some research is being done to try to separate the possible therapeutic effects of cannabis from the psychotropic effects. Other research has shown in recent years the presence of a cannabinoid type receptor in the human body, and the existence of an endogenous cannabinoid. (These are mainly in the brain.) It is possible that synthetic cannabinoids could be developed that minimise toxicity and



maximise therapeutic benefits. Pure THC is already available as a prescription medicine, but crude cannabis smoked in cigarettes does not qualify as a medicine for the following reasons:

- it varies in composition and quality;
- smoking is an unreliable delivery system;
- it is an unstandardised product for medical use.

4.2 “Should we support smoking foxglove plant to obtain digoxin for heart failure, or yew tree bark to obtain Taxol for breast cancer? If so, supporters of smoked cannabis had better be ready to support smoking tobacco for weight control or anxiety.” (Eric A Voth MD, Chairman, The International Drug Strategy Institute.)

4.3 Further research needs to be undertaken in this field to develop and refine cannabinoids that may have a really useful therapeutic application without unacceptable side effects.

## 5. FURTHER POINTS

### 5.1 *The plan of the legalizers*

We ought to realize that it is the plan and purpose of the drug legalizers to give cannabis a good name by persuading the public to accept it as a medicine. They hope that once it is accepted as a medicine, it will soon become legally available for smoking.

### 5.2 *The tobacco industry*

The tobacco industry also used to advertise cigarettes as medicinal until a stop was put to this. They were said to prevent fatigue, aid digestion and even prevent the common cold. Doctors advocated its use. The same was true of opium and heroin. This led to a drugs epidemic in the USA 100 years ago when there were such things as heroin cough drops. Children have been targeted as with the illegal drugs industry.

### 5.3 *Financial aid*

There is another fact to consider, a multi-billionaire financier, George Soros has given tens of millions of dollars to support pro-drugs movements. The latest figure given me by Peter Stoker of Positive Prevention Plus, is that he has given \$60 million in recent years for this purpose. Anti-drugs movements are struggling to campaign with virtually nothing, whilst the drug-legalizers are awash with money.

### 5.4 *The Media*

The media too must be mentioned. Today they do not merely report the news, but they try to advocate new ways and new laws. This is called media advocacy. The media is largely in the hands of a few people who own newspapers, publishers and television networks. Letters to newspapers against the use of cannabis just do not get published, whilst the media portrays cannabis as “good for what ails you”.

## 6. CONCLUSION

Decisions on the use of cannabis as a medicine must be based on scientific evidence, not politics or media advocacy, nor by the voting of a scientifically ignorant populace as in California and Arizona. The public feel compassion for those who are ill, but are scientifically ignorant.

## 7. NOTE

Dronabinol, Marinol and Nabilone are all synthetic formulations of the cannabinoid delta-9-THC.

### **Supplementary Memorandum by David Copestake**

#### **CANNABIS ADDICTION, DEPENDENCE AND TOLERANCE**

### 1. INTRODUCTION

1.1 Advocates of cannabis use have generally claimed that it is non-addictive and therefore harmless. During the 1960s and 70s in Britain, a general opinion amongst people who thought they were informed was that cannabis was not a drug of addiction because there was an apparent absence of tolerance to the effects of the drug, and of a withdrawal symptom as seen in alcohol and opioid addiction. Yet many witnesses from countries with a long history of cannabis use were saying that cannabis was definitely addictive.

1.2 For example, at the Second Opium Conference of the League of Nations 1925, hashish (cannabis resin) was included in the list of narcotics at the suggestion of the Egyptian delegate who said: "Taken thus occasionally and in small doses, hashish perhaps does not offer much danger, but there is always the risk that once a person begins to take it, he will continue. He acquires the habit and becomes addicted to the drug, and, once this has happened, it is very difficult to escape. Notwithstanding the humiliations and penalties inflicted on addicts in Egypt they always return to their vice. They are known as "hashashees", which is a term of reproach in our country, and they are regarded as useless derelicts."

1.3 Joel H Kaplan, a psychiatrist commanding an American medical detachment team in Vietnam, discovered that many soldiers who thought that they would use marijuana only whilst they were in Vietnam were unable to give it up when they came to the end of their tour. There were cases of soldiers who signed up for a second tour because of the readily available drug supply throughout Vietnam. Dr P A L. Chapple in a study of 80 cannabis users found that large numbers became dependent on the intoxicating effects to such an extent that they would not be willing to live without it and would go to any lengths to get it.

1.4 In the late 1970s and early 80s there arose a more liberal definition of addiction and a concept of dependence was applied to psychoactive drugs. This placed less emphasis upon tolerance and withdrawal symptoms and more on symptoms of compulsion to use, the high importance of the drug in the user's life, and rapid reinstatement of dependence after abstinence. This new concept influenced the development of the Third Revised Edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (1987) (DSM-111-R).

## 2. DEFINITION AND RECOGNITION OF DEPENDENCE

2.1 DSM-111-R established three requirements for a diagnosis of substance abuse:

- a pattern of pathological use;
- impairment in social or occupational functioning due to substance abuse; and
- a duration of at least one month.

2.2 There are nine criteria for a diagnosis of psychoactive substance dependence (any three need to be present for the diagnosis), but nos 8 and 9 are not required in the case of cannabis and hallucinogens. The seven relevant are:

1. the substance is often taken in larger amounts or over a longer period than the person intended;
2. there is a persistent desire or one or more unsuccessful efforts to cut down or control substance use;
3. a great deal of time is spent in activities necessary to get the substance (eg, theft) taking the substance . . . , or recovering from its effects;
4. frequent intoxication or withdrawal symptoms when expected to fulfil major role obligations at work, school, or home . . . , or when substance use is physically hazardous . . . ;
5. important social, occupational, or recreational activities given up or reduced because of substance use;
6. continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance; and
7. marked tolerance.

2.3 Dr M S Gold points out that marijuana dependency may masquerade as a wide variety of complaints, most being non-specific: sleeplessness, depression that may range from mild to severe, difficulties at school or at work, impaired social functioning and so on. Often the person will not volunteer cannabis use, or may deny it. Also, the person often believes cannabis use is a consequence of the problem rather than the cause of it.

2.4 Gold is not too happy with DSM-111-R because from a doctor's point of view, waiting for the criteria to be fulfilled may lead to a delay in treatment, as marijuana dependency often has an insidious onset. Further he points out that the criteria are subjective and doctors interpret them very differently. The Fair Oaks Hospital Drug and Rehabilitation Program in the US has developed a series of behavioural, social and medical cues to alert the doctor to ask more questions and order laboratory tests.

## 3. CLINICAL AND OBSERVATIONAL EVIDENCE ON DEPENDENCE

3.1 The Australian National Drug Strategy study 1995 reported that during the 1980s evidence began to emerge that there had been an increase in the number of persons seeking help with cannabis as their major drug problem. For instance 35,000 patients sought treatment in the US in 1981 for drug problems in which "cannabis was their primary drug", an increase of 50 per cent over three years. Many of these patients behaved "as if they were addicted to cannabis" and they presented "some of the same problems as do compulsive users of other drugs". (Now, some 100,000 seek treatment in the US each year.)

3.2 Sweden, which has had a long history of hashish use, has also experienced an increase in numbers of heavy hashish users presenting to treatment services for assistance with problems caused by its use. These



patients reported that they had been unable to stop using cannabis after making several unsuccessful attempts to stop or cut down. Tunving and colleagues have described their experience of treating these, and described how they were frequently intoxicated, often every day and that they continued cannabis use in spite of recognising its adverse effects such as sleeplessness, depression, diminished ability to concentrate and memorise, and the blunting of emotions.

3.3 The Australian Report cites evidence from several sources suggesting that cannabis dependence is a fact. This has emerged from the observational study of regular cannabis users, and some studies have been based on the DSM-111-R criteria.

3.4 A single case study by Solowij and colleagues has shown a dramatic normalisation of brain event-related measures when the subject was tested in an acutely intoxicated state prior to the cessation of use. This suggests a basis for the physical dependence component of cannabis use.

3.5 Cannabis dependence may result in the following withdrawal symptoms after cessation of use:—anxiety, depression, sleep and appetite disturbances, irritability, tremors, diaphoresis, nausea, muscle convulsions and restlessness.

#### 4. RECENT ANIMAL STUDIES ON DEPENDENCE AND THE “REWARD” SYSTEM

4.1 Two recent studies in the journal *Science* (27 June 1997) show similarities between the effects of cannabis on the brain and those of highly addictive drugs such as cocaine, heroin, alcohol and nicotine. Ingrid Wickelgren has summarised the results and importance of the finding in that same issue.

4.2 One study traces the symptoms of emotional stress caused by cannabis withdrawal to the same brainchemical, a peptide called corticotropin-releasing factor (CRF), that has been linked to anxiety and stress during opiate, alcohol and cocaine withdrawal. The second shows that THC results in the same biochemical event that seems to reinforce dependence on other drugs such as nicotine and heroin—the release of dopamine in part of the brain’s “reward” system.

4.3 These studies provide evidence that cannabis acts on the same neural substrate and has the same effects as drugs which are known to be highly addictive. Wickelgren states that experts conclude that these results provide the first neurochemical basis for a cannabis withdrawal syndrome, and one with a strong emotional component that is shared by other addictive drugs.

4.4 Addictive drugs have rewarding or reinforcing effects that keep people and animals “coming back for more”. A key event in this action is the release of dopamine in the brain. This is an important part of the “reward” system, and addictive drugs are thought to lead to compulsive behaviour because they unleash a dopamine surge. Now it has been demonstrated that cannabis (THC) can induce the dopamine rush. The magnitude of the surge was similar to what the researchers saw when they gave heroin to another set of rats. These researchers also found that naxalone, a drug that blocks brain receptors for heroin and other opiates, prevents THC from raising dopamine levels. This provides another parallel with heroin.

4.5 The researchers suggest that cannabis activates opiate receptors indirectly by causing the release of an endogenous opiate, a heroin-like substance made in the brain. This could provide a biological basis for the gateway hypothesis in which using cannabis is thought to cause some people to go on to harder drugs by priming the brain to seek substances like heroin that act in a similar way.

#### 5. TOLERANCE

5.1 For many years it was believed that there was no tolerance to cannabis. However, since the mid 1970s evidence has emerged from human and animal studies of the development of marked tolerance to a wide variety of cannabis effects—such as cardiovascular effects and the subjective high. In one study by Georgotas and Zeidenberg the five subjects of the study, who for a four week period smoked an average of 10 joints a day, experienced the following effects. “Although initially they found the marijuana to be of good quality, they now found it much weaker and inferior to what they were getting outside. They felt it did not make them as high as often as they were accustomed.”

5.2 Some researchers have suggested that cannabis tolerance is dispositional—that is, caused by changes in the way the drug is stored or metabolized. Others say that tolerance is primarily functional, a conclusion supported by studies showing similar patterns of drug distribution and metabolism in both heavy and light users.

5.3 The significance and importance of this is that tolerance to the intoxicated high state encourages users to escalate their cannabis doses.

#### 6. CONCLUSION

6.1 On the basis of this evidence I conclude that there is a cannabis dependence syndrome such as defined in DSM-111-R. There is also good evidence that heavy cannabis use can produce tolerance and withdrawal symptoms and that some users find difficulty controlling their drug use in spite of adverse personal consequences.

6.2 Not all cannabis use results in dependence and even chronic users may eventually stop using the drug on their own. Gold states that marijuana dependency is extremely difficult to treat successfully, and treatment must begin as early as possible. He states further "the short-term use of marijuana can still cause irreversible social, psychiatric, and medical consequences, such as poor academic performance, trauma related to automobile accidents or other types of accident, and/or criminal charges. It is impossible to predict whether a given case will progress or resolve on its own. For that reason, it is important to treat all cases of marijuana use as potentially addictive." It is also extremely expensive to try and treat those dependent upon drugs, and this should be remembered when considering legislative policy.

*David R Copestake*

*3 May 1998*

**Memorandum by Dr Angela Coutts, Biomedical Sciences, University of Aberdeen**

1. My own work concerns the neural and biological mechanisms that underlie the effects of cannabis and cannabinoid drugs, including the mechanisms underlying the development of tolerance. However, this work does not address the specific issues under study by Sub-Committee I on Cannabis, though it is anticipated that increasing our understanding of the mechanism of action of these drugs will lead to a better appreciation of the development of tolerance to drugs of abuse and to the design of new cannabinoid drugs with greater potential of therapeutic use without the attendant psychotropic and dependence-forming attributes.

2. In the literature are studies describing the perceived effects of smoking cannabis in ameliorating the symptoms of multiple sclerosis. There is also anecdotal evidence of the beneficial effects of cannabis where conventional therapy has been unsuccessful. This latter evidence is not scientifically reliable. I believe that there is a strong case to be made for promoting scientifically controlled clinical trials for the therapeutic benefit of cannabinoid drugs.

*12 March 1998*

**Memorandum by the Department of Complementary Medicine, University of Exeter**

**CANNABIS AND CANNABINOIDS FOR SPASTICITY IN MULTIPLE SCLEROSIS:  
A BRIEF REVIEW**

1. In multiple sclerosis (MS), there is an ongoing need for palliative therapies to improve clinically defined or perceived symptoms of the disease. Spasticity is a common clinical problem in patients with MS. As well as contributing to disability by impairing mobility, spasticity causes distressing symptoms, including muscle spasms and pain. The relief of spasticity would reduce discomfort and facilitate nursing care or hygiene. However, few agents have been shown to be both "safe" and effective in treating spasticity, and many patients with MS find that currently available muscle relaxants are inadequate in controlling pain, stiffness, muscle rigidity and activity restrictions associated with muscle spasticity. For some patients, the adverse effects associated with the use of such drugs also cause significant problems.

2. There are now several anecdotal reports, and survey data to suggest that oral or inhaled cannabis can reduce or ameliorate spasticity in patients with MS. In one report, improvements in spasticity, ataxia and tremor reported by the patient were found to be reproducible and quantifiable in a laboratory situation.

3. Oral administration of delta-9-tetrahydrocannabinol (THC), the predominant constituent of cannabis thought to be responsible for the psychoactive effects of cannabis, has been tested in four small trials in patients with MS. In a double-blind, placebo-controlled study involving nine patients with spasticity related to MS, oral THC 5 or 10 mg significantly reduced spasticity scores three hours after administration ( $p < 0.01$ ). Oral THC 5-15 mg was also reported to lead to both subjective and objective improvements in motor coordination in two of eight MS patients with disabling tremors and ataxia. A double-blind, placebo-controlled, crossover study in 13 individuals with MS and spasticity showed that the level of spasticity reported by patients was reduced with doses of THC  $\geq 7.5$ mg daily. However, there was no difference in levels of spasticity between groups according to the physicians' assessments. Greenberg et al reported subjective improvements in some patients after smoking marijuana in a randomised, double-blind, placebo-controlled trial involving 10 patients with MS and 10 healthy volunteers. However, cannabis was reported to impair posture and balance in all subjects, causing greater impairment in patients with MS. More recently, an open-label, multiple-dose pilot study investigating the effect of orally (10-15mg) and rectally (2.5-5mg) administered THC on spasticity was conducted in two patients. Both oral and rectal THC reduced spasticity, rigidity and pain, resulting in improved active and passive mobility.

4. The synthetic cannabinoid nabilone has also been reported to provide benefit in an "n-of-1" trial in a patient with MS. In this simple, yet placebo-controlled, double-blind, crossover study, muscle spasm, general well-being and frequency of nocturia were all found to be improved during treatment phases; whereas these benefits disappeared when placebo was given.

5. The evidence is also reviewed in the British Medical Association's report on the therapeutic uses of cannabis. None of the studies described provides conclusive evidence of the effectiveness of cannabis and its



individual constituents for symptom improvement in patients with MS. However, there is sufficient evidence to justify further, more extensive and rigorous investigation. A randomised, controlled trial, properly blinded and with a sample size calculated to derive statistical validity, could determine whether or not cannabis has a clinically relevant, specific effect (as opposed to a placebo effect) on spasticity. Such a trial could also indicate whether a genuine potential therapeutic use for cannabis is being ignored.

6. The Department of Complementary Medicine within the Postgraduate Medical School at the University of Exeter has been planning a study of a THC-standardised oral cannabis preparation for spasticity associated with MS. The principal investigators are Jo Barnes, a research pharmacist, and Dr Will Honan, consultant neurologist at the Royal Devon and Exeter Hospital. Funding has now been obtained from the University of Exeter for a pilot study in around 30 patients; it is planned that the study will start in September/October 1998. Ms Barnes has the necessary approvals for the study (ethical approval from the Exeter Research Ethics Committee, Medicines Control Agency approval; a Home Office research licence for cannabis has been granted in principal and will be issued when there is a definite start date for the study). It is emphasised that this is a pilot study. It is intended that the study will provide data which can be used for a sample size calculation for a full-scale study with adequate power to test the null hypothesis that the effects of an orally administered, THC-standardised cannabis preparation on spasticity associated with MS are equivalent to those of placebo.

This summary is submitted on behalf of the Department of Complementary Medicine, University of Exeter.

*Jo Barnes BPharm, MRPharmS, MIFA*  
Research Fellow Department of Complementary Medicine  
Postgraduate Medical School University of Exeter

25 March 1998

#### **Supplementary Memorandum by the Department of Health**

The Committee has requested information concerning the possibility of leakage of drugs which are prescribed in the treatment of drug misuse impacting on the availability of cannabis.

Substitute prescribing is in most cases used in the treatment of opiate addiction. We consider that it is unlikely to be an issue in relation to cannabis misuse as cannabis cannot be supplied legally, not least as part of a programme of treatment.

Methadone is the most commonly used form of substitute prescribing in the UK, and is an established substitute drug therapy used internationally to treat people who are opiate dependent. Methadone can be prescribed for a range of treatments. Prescribing has expanded in recent years and is used not only for detoxification, but for stabilisation and longer term therapies.

The benefits of substitute prescribing, confirmed by international research and practical experience in the UK, are well documented and include:

- limiting damaging injecting behaviour and minimising harm;
- stabilising the chaotic lifestyle of drug misusers;
- reducing the spread of HIV through intravenous drug misuse;
- improving physical and mental health by bringing misusers into touch with the appropriate services;
- taking drug misusers out of the hands of drug pushers; and
- removing the need for drug misusers to fund the habit, thus potentially reducing drug-related crime.

The 1997 Task Force report, an independent review of drug treatment services in England, confirmed these benefits. It made several recommendations for developing prescribing and dispensing arrangements and for the management and structure of treatment programmes.

The evidence from the Task Force report suggests a disproportionate increase in methadone deaths amongst drug misusers who were not prescribed methadone nor notified to the Home Office. The presumption is that they were obtaining supplies either by theft or from diversion—leakage—from legitimate sources.

The Task Force made several recommendations aimed at improving current methadone prescribing regimes and reducing the risks from leakage. These include daily dispensing, supervised consumption and regular reviews.

Clinical guidelines for doctors dealing with drug misusers were issued in 1991. These are currently being revised, and will provide up-to-date advice for doctors who prescribe methadone. The revised guidelines are still being developed by a working group which is chaired by Professor John Strang of the National Addiction Centre. The guidelines are likely to address issues surrounding the leakage of prescribed drugs and compliance from patients on a methadone prescription. The revised guidelines, which will be available to all doctors in the UK, will be published later this year.

There is, however, the cannabinoid *Nabilone* which is licensed for marketing in the UK. Leakage may arise as an issue in relation to *Nabilone*. Nevertheless, this is highly unlikely as the licence for *Nabilone* is for supply to hospitals only and, therefore, would be dispensed only by hospital pharmacies. Furthermore, the Product Summary Characteristics (which were sent to the Committee under cover of Richard Kornicki's letter of 19 May) recommend that "Prescriptions should be limited to the amount necessary for a single cycle of chemotherapy (ie, a few days)."

Please let me know if the Committee requires any further information.

*Alastair Thomas*  
Drugs Misuse Teams

19 June 1998

#### **Memorandum by the Evangelical Coalition on Drugs Executive Committee**

I am writing on behalf of the Evangelical Coalition on Drugs Executive Committee in response to the invitation to submit written evidence about cannabis.

The ECOD Executive represents some 75 groups and individuals affiliated to the Evangelical Alliance and who have a special interest in the area of illegal drugs. Many of its member groups are rehabilitation/counselling institutions and others carry out "street work" with young people including those using illegal drugs.

The Evangelical Alliance has a membership which represents over one million people in different churches and Christian organisations throughout the country.

Rather than re-summarise existing work, we have chosen to submit a summary of research about cannabis written by David Copestake BA (psych) BD MPhil called "Cannabis and Mental Function" (*not printed*). We feel that this adequately summarises our understanding of the balance of the literature and provides information about the questions the Sub-Committee is asking.

Our considered conclusions are:

1. Agreement with the British Medical Journal's editorial of 4 April 1998 which pointed out that cannabinoids have the potential for medical use. We are happy to accept this view subject to the setting up of controlled clinical trials and the usual safeguards in accepting new medicines.

2. However, we consider that the balance of current scientific evidence confirms the necessity to maintain legal prohibition for social use. There is a growing volume of scientific evidence which supports this view and, in particular, we would direct the committee to the "Cannabis and Mental Function" document which we have enclosed. We note that there have been recent press reports linking illegal drug consumption (especially cannabis) with road accidents and we consider that this is a significant further pointer to the need to maintain legal prohibition for non-medical use.

3. We also feel that the terms of reference for the committee are too narrow, because to consider only the psychopharmacological evidence without looking at the broader sociological factors is unhelpfully restrictive. The cannabis debate has as much a social as a scientific dimension.

We hope that this will be helpful in your considerations.

*David Partington*  
Chairman

8 May 1998

#### **Memorandum by the Forensic Science Service**

##### **TETRAHYDROCANNABINOL (THC) CONTENT OF CANNABIS**

Further to our recent telephone discussion, I can provide you with the following information.

Cannabis resin, a wholly imported material, has a mean THC content of 4-5 per cent, although the range is from less than 1 per cent to around 10 per cent. This pattern has remained unchanged for many years.

Herbal cannabis may be seen in a number of forms, but the material most commonly seized by Police and Customs in the UK has been imported in the form of compressed blocks; the mean THC content is also 4-5 per cent with a range similar to that of resin.

Until about eight years ago, "home grown" cannabis was a poor quality product often grown in greenhouses or on windowsills and normally for personal use. However, the introduction of a number of horticultural techniques has led to the widespread and large scale domestic indoor cultivation of cannabis with a much higher THC content. These techniques include hydroponics, artificial lighting, control of "day" length, heating and ventilation, cloning of "mother plants", and, perhaps most importantly, the development of plant varieties which produce higher THC levels. The mean THC content of so-called hydroponic cannabis is close to 10 per cent with a range extending to over 20 per cent.



The attached diagram shows the frequency distribution of THC levels in cases examined in the FSS in the period 1996 to 1998. This only includes those few cases where the THC content was requested by the submitting Officer, but I have no reason to believe that the data are not representative. "Hydroponic" refers to cannabis intensively cultivated in the UK, while "Compressed" refers to imported, traditionally cultivated, material. In both cases the THC content refers essentially to the flowering tops of female plants.

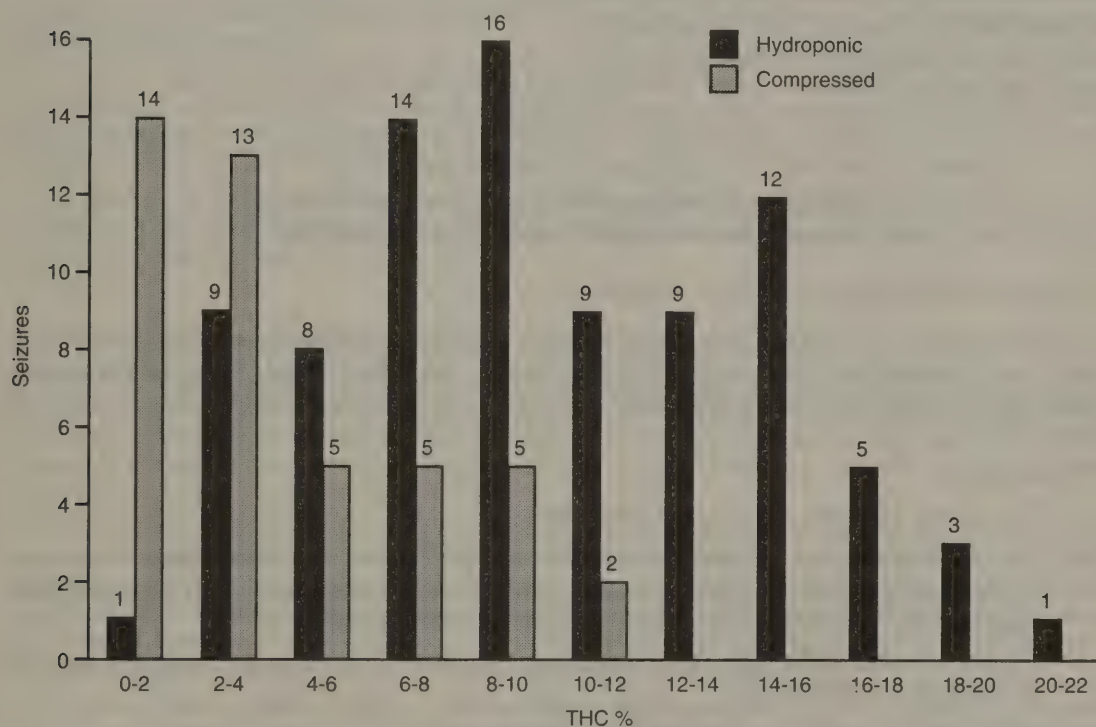
I trust that this is helpful to the Science and Technology Committee. There is no objection to the Committee making this information publicly available.

*Dr L A King*

Drugs Intelligence Unit Manager

8 May 1998

### The Tetrahydrocannabinol (THC) content of herbal cannabis (1996-98)



### Memorandum by Professor Keith Green, Medical College of Georgia, USA

1. I wish to address some comments on deliberations concerning the possible use of cannabis and its derivatives for medicinal purposes. These views arise from my involvement in investigations of the effects of cannabinoids and related compounds on the eye for over 26 years.

2. In 60 to 65 per cent of the population that smokes cannabis (plant material) or orally takes marijuana (or THC), the intraocular pressure (IOP) falls by an average of 25 per cent. The range is from -45 per cent to +5 or 10 per cent. This immediate effect lasts for a total of three or four hours, regardless of the dose, before return to baseline IOP. Peak fall in IOP occurs at one and a half to two hours; the dose simply affects the amount of reduction in IOP.

3. In order to reduce the elevated IOP of glaucoma to a level where it would not rise to baseline levels, it would be necessary to smoke about 10 marijuana cigarettes per day. Glaucoma is a lifetime disease and is typified by an elevated IOP that must be controlled to low values. Smoking 3,650 marijuana cigarettes per year would expose the recipient to excess tars and volatile chemicals at a greater concentration than found in tobacco products. Substantial adverse toxicity to body tissues would occur with intake of that level of marijuana.

4. Accompanying the physiological effect on the eye are cognitive effects that are more pronounced in an elderly population (where glaucoma primarily occurs) and in persons who smoke marijuana continually (as would be needed to regulate IOP).

5. The above findings on IOP have been confirmed in over 300 persons with normal or elevated IOP. Numerous animal studies in rabbits, dogs, cats and monkeys have confirmed the physiological effects.

6. Future use of cannabinoids that do not have euphoric effects, that currently exist and are in animal and clinical trials for other purposes would be advantageous to use to reduce IOP.

7. Based upon the above, the evidence for permitting medical use of cannabis in the treatment of glaucoma is poor and counter-indicates this use.

8. Cannabis, the plant material, cannot be standardised since it inherently varies depending upon the site and conditions of growth, regardless of the seed origins. It cannot, therefore, meet even the most meagre of requirements for definition as a medicine. Individual cannabinoid-like chemicals can be well characterised chemically.

9. The evidence for smoking oral or topical cannabinoids that have low euphoria-inducing capability, but a good effect in reducing IOP is convincing. Efforts should be placed in the latter category to identify pure chemicals that have favourable features in the reduction of glaucomatous IOP.

This evidence is submitted on an individual basis and reflects the opinion of the author based upon considerable experience in glaucoma and marijuana.

*Keith Green, PhD (St Andrews), DSc (St Andrews)*  
Regents' Professor Director of Ophthalmic Research

21 April 1998

**Memorandum by Professor Wayne Hall, Executive Director,  
National Drug and Alcohol Research Centre, Australia**

**1. *The Health and Psychological Effects of Cannabis***

1.1 The following is a summary of the most probable adverse and psychological effects of cannabis updated from a summary previously published in Hall, Solowij and Lemon (1994). A detailed justification for these conclusions can be found in that source and a briefer version in the attached paper by Hall and Solowij (1998).

**1.2. Acute effects:**

- 1.2.1 anxiety and panic, especially in naive users;
- 1.2.2 impaired attention, memory and psychomotor performance while intoxicated;
- 1.2.3 possibly an increased risk of accident if a person drives a motor vehicle while intoxicated with cannabis, especially if cannabis is used in combination with alcohol;
- 1.2.4 an increased risk of psychotic symptoms among those who are vulnerable because of personal or family history of psychosis.

**1.3 Chronic effects remain uncertain but the most probable are:**

- 1.3.1 symptoms of chronic bronchitis and histopathological changes that may be precursors to the development of malignancy caused by smoking cannabis;
- 1.3.2 a cannabis dependence syndrome characterised by an inability either to abstain from or control cannabis use;
- 1.3.3 subtle impairments of attention and memory that persist while the user remains chronically intoxicated, and that may or may not be reversible after prolonged abstinence.

**1.4 Among possible adverse effects that remain to be confirmed are:**

- 1.4.1 an increased risk of a low birth-weight baby if used during pregnancy;
- 1.4.2 an increased risk of: cancers of the oral cavity, pharynx, and oesophagus; leukemia among offspring exposed while in utero;
- 1.4.3 impaired educational attainment in adolescents and under-achievement in adults in occupations requiring high level cognitive skills.

**1.5 Groups at higher risk of experiencing these adverse effects include:**

- 1.5.1 adolescents with a history of poor school performance, who initiate cannabis use in the early teens. They are at increased risk of using other illicit drugs and of becoming dependent on cannabis;
- 1.5.2 women who continue to smoke cannabis during pregnancy may increase their risk of having a low birth weight baby;
- 1.5.3 persons with asthma, bronchitis, emphysema, schizophrenia, and alcohol and other drug dependence, whose illnesses may be exacerbated by cannabis use.



## 2. *Relationship between harm, route of administration and preparation of cannabis*

2.1 Smoking is the predominant method of using cannabis in Australia and probably elsewhere. It is likely to remain so because users experience difficulty titrating the dose of THC when it is taken orally for recreational or therapeutic reasons (Hall et al, 1994).

2.2 The clearest harm arising from cannabis use is the respiratory risk of smoking it and exacerbation of the respiratory risks of cigarette smoking, a habit that is much more common among cannabis than non-cannabis users. These include: chronic bronchitis, pathological changes in lung tissue that may be precursors of carcinoma, and impaired immunity in the respiratory system (see Hall, 1998 attached).

2.3 Concern has been expressed about the increased harms arising from the use of cannabis of high THC content. The extent of increase in the THC content of cannabis has been contested but even if there has been an increase in THC content, in more potent forms of cannabis need not inevitably have more adverse effects on users' health than less potent forms. Indeed, it is conceivable that increased potency may have little or no adverse effect if users are able to titrate their dose to achieve the desired state of intoxication (eg Kleiman, 1992; Mikuyira and Aldrich, 1988). If users do titrate their dose, the use of more potent cannabis products would reduce the amount of cannabis material that was smoked, thereby marginally reducing the respiratory risks of cannabis smoking.

2.4 If users are not able to titrate their dose of THC, higher average doses of THC may produce an increase in the adverse psychological effects of acute use, especially among naive users, which could discourage further experimentation. Among experienced cannabis users, an increased average THC dose may increase the risk of accidents among those who drive while intoxicated, and the risk of developing dependence.

2.5 Studies of the ability of experienced users to titrate their dose of THC would contribute to an evaluation of this issue. So too would the inclusion of questions about the form of cannabis and its perceived potency in sample surveys.

## 3. *Tolerance, Withdrawal and Dependence*

3.1 There is good evidence that humans and animals in laboratory studies develop tolerance to the effects of THC (Hall et al, 1994). The laboratory evidence is supported by the preference of regular cannabis users for the more potent forms of cannabis (Didcott et al, 1997). There is also reasonable evidence of a withdrawal syndrome in some heavy cannabis users, although it is of variable severity, as is the case with withdrawal symptoms from nicotine, alcohol and heroin.

3.2 By popular repute, cannabis is not a drug of dependence because it does not have a clearly defined withdrawal syndrome. There is, however, little doubt that some users want to stop or cut down their cannabis use, find it very difficult to do so, and continue to use cannabis despite the adverse effects that it has on their lives (Hall et al, 1994). Epidemiological studies (eg Anthony et al, 1994) suggest that cannabis dependence in the sense of impaired control over use is the most common form of drug dependence after tobacco and alcohol, affecting as many as one in 10 of those who ever use the drug.

3.3 Some reject the idea of cannabis dependence (eg Zimmer and Morgan, 1997), arguing that the increase in persons complaining of cannabis dependence is a result of drug testing and a cannabis "treatment industry" in the USA. But 80 per cent of the one in 10 of those who have ever used cannabis meet criteria for dependence in population surveys have not been in treatment (Hall et al, 1994). In Australia, cannabis use is highly prevalent, drug testing is uncommon and there is no cannabis treatment industry. Yet treatment services that traditionally treat alcohol and opiate dependence have seen an increase in the number of persons seeking help for cannabis as their primary problem (Hall et al, 1994).

## 4. *Therapeutic Uses of Cannabis and Cannabinoids*

4.1 There is good evidence for the therapeutic potential of THC as an anti-emetic agent. Although uncertainty exists about the most optimal method of dosing and the advantages and disadvantages of different routes of administration, there is sufficient evidence to justify its being made available in synthetic form to cancer patients. In the light of the recent development of more effective anti-emetic agents, it remains to be seen how widely used THC will be for this purpose.

4.2 There is suggestive evidence that THC may be useful in the treatment of glaucoma, especially in cases which have proved resistant to existing anti-glaucoma agents. Further research is clearly required but this should not prevent its use under medical supervision in poorly controlled cases, provided patients make informed decisions about its use in the light of the possible health risks of long-term use.

4.3 There is also suggestive evidence that cannabinoids may be useful as analgesic, anti-asthmatic, anti-spasmodic, and anti-convulsant agents. This warrants pharmacological, experimental and clinical research into their effectiveness. The use of THC as an anti-spasmodic agent in multiple sclerosis may be the most promising use, given the dearth of effective agents for this purpose.

4.4 Much of the case for the therapeutic uses of cannabinoids as other than anti-emetic agents depends upon anecdotal evidence from case histories. This has come to be distrusted as evidence of therapeutic

effectiveness in clinical medicine, especially in the case of chronic conditions which have a fluctuating course of remission and exacerbation.

4.5 Despite good evidence of the therapeutic potential of THC as an anti-emetic and appetite stimulant, it has not been widely used for these purposes. Nor has clinical pharmacological research been undertaken on optimal methods of using these drugs for these conditions.

4.6 Clinical research on the therapeutic use of cannabinoids has been discouraged because THC, the most therapeutically effective cannabinoid to date, also has the psychoactive effects sought by recreational users. The recent discovery of the cannabinoid receptor may help to overcome some of the resistance to research into the therapeutic uses of cannabinoids by holding out the prospect that the psychoactive effects of the cannabinoids can be disengaged from their other therapeutically desirable effects.

4.7 Research on the therapeutic use of cannabinoids has become a casualty of the debate in the United States about the legal status of cannabis. The proponents of its therapeutic uses (many of whom also advocate its recreational use) have argued that smoked marijuana should be available for medical use because this is the most effective mode of delivering THC for some therapeutic purposes. The opponents of such use have countered that marijuana has no therapeutic use since its few uses are better met, either by other more effective drugs which do not have the psychoactive effects of THC, or by the oral delivery of synthetic cannabinoids. They have been supported by medical researchers and practitioners who argue for the therapeutic superiority of pharmaceutically pure drugs which can be given in defined doses.

4.8 The debate about the therapeutic uses of marijuana has been driven by the debate about the legal status of recreational marijuana use. Some of the groups advocating the therapeutic use of cannabis have also been proponents of cannabis legalisation (eg NORML), thereby fuelling the fears of opponents of cannabis use that success in the campaign for "medical marijuana" will be the thin edge of a wedge to legalise cannabis. Some opponents of marijuana use fear that admitting that marijuana, or any of its constituents, have a therapeutic use will send the "wrong message" to youth. They have denied that cannabinoids have any therapeutic effects, and discouraged scientific inquiry into such effects.

4.9 The connection forged between the debates about the legal status of cannabis as a recreational drug and the use of cannabinoids for therapeutic use is spurious. There is a world of difference between the use of controlled doses of a pure drug under medical supervision and the recreational use of crude preparations of a drug. In a rational world, clinical use of pure cannabinoid drugs should not be precluded because crude forms of the drug may be used recreationally.

## 5. *The Strength of the Case for Continued Cannabis Prohibition*

5.1 Evidence on the harms caused by cannabis use, especially chronic long-term cannabis use, remains uncertain. The most probable adverse health effects of cannabis use are those that primarily effect the user, namely, respiratory effects, dependence, exacerbation of psychosis, and cognitive impairment. The available evidence is equivocal on whether cannabis use causes to anyone other than the user, with the most probable effects that remain to be confirmed being an increased risk of motor vehicle accidents if users drive while intoxicated and giving birth to low birth-weight babies if the mother smokes cannabis during her pregnancy.

5.2 Even allowing for the uncertainty about health effects, *on current patterns of use* there is much less harm caused by cannabis than caused by tobacco and alcohol use (Hall, 1995). The uncertainty about the health effects of long-term cannabis use is compounded by the difficulty in predicting the effect that any relaxation of cannabis prohibition would have on current patterns of cannabis use and the harms caused by that use (Hall, Room and Bondy, 1998).

5.3 The debate about cannabis policy is marked by strong inter-generational differences in the perceived seriousness of the health risks of cannabis use. In Australia, persons under the age of 35 have a much more benign view of cannabis use than older adults, reflecting their own and their peers' often relatively benign experiences with the occasional use of the drug (Hall and Nelson, 1995).

5.4 There is strong disagreement between proponents and opponents of cannabis law reform about how the uncertainty about the health effects of cannabis should be resolved for the purposes of making social policy. Those who favour a continuation of existing policy argue that the burden of proof rests with those who favour changes in the law to demonstrate the safety of cannabis use. Those who favour liberalisation of current policy argue that proponents of the status quo have an obligation to justify laws that prevent adults from exercising personal choices about risky behaviour.

5.5 There has been a lack of attention on the part of proponents of liberalisation to specify the type of change that is envisaged. Any serious consideration of a legal cannabis market must specify under what conditions and regulations it would be made available. Would the type of market for cannabis be more like that for: coffee, cigarettes or alcohol?

5.6 Reasonable fears of creating a large cannabis industry with an interest in promoting the use of its product, have prompted some to advocate a "grudging tolerance" of cannabis use (Kleiman, 1992). On this policy, society would tolerate cannabis use by adults, while discouraging its use by restricting where and when it could be used, much as some Western societies grudgingly tolerate prostitution. The difficulty is that "grudging tolerance" presupposes a quasi-legal market to meet the needs of those who choose to use cannabis.



It is unlikely that this need will be fully met by users growing their own. International treaties are an obstacle to the legalisation of cannabis markets since most Western societies are signatories to international agreements that prohibit the use of cannabis.

5.7 "Depenalisation" (the removal of criminal penalties for personal use of cannabis) is often presented as a compromise that preserves the symbolism of prohibition without imposing criminal penalties on the young persons who are caught contravening the law. It has been seen as a more reasonable policy than imprisoning persons for an offence that largely harms themselves, especially when we do not routinely do so for drink drivers who do put others at risk. Fines are also effective in discouraging use. The depenalisation of cannabis does not appear to have led to increased use in South Australia, probably because it brings law into line with practice (Donnelly, Hall and Christie, 1995).

**Memorandum by Professor John Henry FRCP FFAEM, Imperial College School of Medicine, also on behalf of the Royal College of Pathologists**

**1. WHAT ARE THE PHYSIOLOGICAL EFFECTS (IMMEDIATE, LONG-TERM AND CUMULATIVE) OF TAKING CANNABIS, IN ITS VARIOUS FORMS?**

*1.1 Immediate Effects*

1.1.1 The immediate physiological effects are marked vasodilatation (dilation of blood vessels), which is associated with reddening of the conjunctival membrane of the eye with warmth of the skin and an increase in heart rate (which may be as high as 160 beats per minute) and a fall in blood pressure on standing (which may be enough to cause dizziness or unsteadiness).

1.1.2 Intraocular pressure is reduced, the bronchi are dilated, the mouth becomes dry (which may lead to the sensation of thirst), and there is an increase in appetite and constipation.

1.1.3 These immediate effects are marked and occur to a noticeable effect in the great majority of people given cannabis.

*1.2 Long Term and Cumulative Effects*

1.2.1 Although there is a degree of tolerance to the physiological effects of cannabis, the above immediate effects will occur each time cannabis is used. Testosterone levels and sperm count in men and fertility in women, gestational time and foetal birthweight are all reduced; measures of intelligence are lower at three years in children born of cannabis smokers. One form of leukaemia is 10 times more common in infants born of cannabis smokers. There is little documentation concerning other long term physiological effects. There is a tendency for the effects of cannabis to be cumulative because of its slow elimination by the body.

1.2.2 Cannabis contains tars so that when it is smoked, risks similar to those associated with cigarette smoking are also incurred. These include chronic respiratory diseases and cancers of the upper respiratory tract. However, there are few studies on the effects of smoking marijuana alone because the majority of cannabis users smoke tobacco also.

**2. WHAT ARE THE PSYCHOLOGICAL EFFECTS?**

2.1 The short term psychological effects of cannabis include relaxation, euphoria, impaired motor co-ordination, slowed reaction time and heightened sensory perception. The perception of the passage of time is slowed. Anxiety and depressed mood may also occur. Higher doses may cause apprehension, suspiciousness, hostility, confusion, memory impairment, depersonalisation, derealisation and hallucinations. Tolerance occurs to the psychological effects of cannabis so that memory and learning are impaired. "Flashbacks" (a recurrence of the experience while under the drug) can occur following chronic cannabis use. The recognition and acquisition processes involved in the storage of short term memory are affected.

2.2 The use of even relatively modest amounts of cannabis can result in a deterioration in co-ordination and reaction time to make operations such as driving and flying hazardous. Several studies have implicated cannabis in fatal and non-fatal traffic accidents. These deleterious effects on psychomotor performance may go unrecognised by the user because of an increase in the level of awareness of sensations. (In one study only one out of 89 airline pilots given cannabis was aware that their performance was impaired). Although many people claim that cannabis use leads to an amotivational state, there are no reliable scientific data to support its existence. However it is possible that some regular users become apathetic due to the accumulated intoxicant effects of the drug.

2.3 The relationship of psychosis to cannabis is controversial. Heavy users may become psychotic but schizophrenic thought disorder is usually absent. The best known study investigating the relationship between schizophrenia and cannabis in 45,570 Swedish conscripts found a dose related link between cannabis use and subsequent schizophrenia. However, this is an epidemiological relationship, not a causal one.

### 3. TO WHAT EXTENT IS CANNABIS ADDICTIVE?

The cessation of cannabis use in chronic users is often followed by withdrawal symptoms such as irritability, restlessness, loss of appetite, nausea and insomnia, which indicates a degree of addiction. However, it does not seem to be associated with as marked a craving or psychological dependence as nicotine or alcohol. This may be related to the fact that it persists in tissues for a considerable period of time, thus acting as a buffer against acute withdrawal symptoms.

### 4. TO WHAT EXTENT DO USERS DEVELOP TOLERANCE TO CANNABIS?

As mentioned above, there is mild tolerance to the physiological effects, and greater tolerance to the psychological effects.

### 5. WHAT IS THE EVIDENCE THAT CANNABIS IN ITS VARIOUS FORMS HAS VALUABLE MEDICINAL ACTIONS?

#### 5.1 *In the treatment of which diseases?*

A recent review by the British Medical Association (1997) has shown that cannabis has been proposed in the treatment of a wide range of illnesses.

#### 5.2 *How rigorous is the evidence?*

In most cases, the beneficial effects of cannabis and its constituent chemicals are less than those of other established pharmaceutical agents (eg in the management of glaucoma, asthma, and pain relief).

#### 5.2 *Is there a case for promoting clinical trials even if the current level of control is maintained?*

I believe there is a case for controlled clinical trials, but these should be of cannabinoids in a form other than cigarettes, and there is no need for any exceptions to be made because the mechanisms for study already exist, and at least one preparation (Nabilone) is currently prescribable in the UK.

ON THE BASIS OF THE ANSWERS TO THESE QUESTIONS,

### 6. HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF PERMITTING MEDICINAL USE?

Currently the scientific evidence of benefit is too weak to support further indications for the use of cannabinoids. There are several conditions in which cannabis is used by sufferers (eg multiple sclerosis and rheumatoid arthritis) with claims of marked subjective benefit, but any objective scientific evidence of benefit is lacking. Cannabinoids may have beneficial effects on symptoms such as pain, muscle spasm and disturbed bladder function. Controlled trials are needed to assess benefit and to determine the pharmacological effects of psychoactive and non-psychoactive cannabinoids.

### 7. HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF MAINTAINING PROHIBITION OF RECREATIONAL USE?

The effects on behaviour, co-ordination and reaction times, as well as the potential cumulative hazards from the effects of smoking, argue against a relaxation of the current prohibition.

12 May 1998

#### **Memorandum by Dr Anita Holdcroft, Reader in Anaesthesia, Imperial College of Science, Technology and Medicine, Anaesthetic Department, Hammersmith Hospital**

The completion of a double blind, placebo controlled, randomised clinical trial [1,2] into the effects of an oil of cannabis preparation on pain and inflammation provides the following evidence:

1. The oral route of administration is acute and long-term studies is feasible.
2. The natural preparation of oil of cannabis containing tetrahydrocannabinol and cannabidiol, both active cannabinoids, was not as effective orally as by inhalation. The inhalational route requires development (eg a spray aerosol) but not with combustion (ie avoid smoking).
3. The study of a cannabis user as a patient was difficult. Wash out of cannabis was not complete and maintenance of compliance was time consuming. Cannabis naïve subjects are required.
4. Tolerance seemed to become a problem with long term chronic use. However, this could not be properly tested.
5. The natural preparation of cannabis used in the study had a highly significant effect in reducing morphine consumption. This is clinically important. Its use as an analgesic requires further



investigation. Although no anti-inflammatory effects could be measured, we would consider that prior use of cannabis by the patient could have interfered with this part of the investigation.

There is now an explosion of information from basic sciences (non-clinical) on cannabinoid use which supports the use of natural or synthetic preparations to treat clinical pain and inflammation. There are both central and peripheral cannabinoid receptors with naturally occurring ligands, and both agonist and antagonist pharmacological agents are being developed to act at these receptor sites. Central antinociceptive effects of cannabinoids have been well documented. Peripheral receptors have been located in many organs, such as the spleen and lymph nodes. Their activity may have a significant role in the inflammatory response that generates pain. Within the specialty of anaesthesia the only analogous group of drugs is the non-steroidal anti-inflammatory analgesics such as ibuprofen and aspirin. These drugs are mild to moderate analgesics and reduce inflammation but have serious side effects such as gastrointestinal haemorrhage and renal failure which limit use in postoperative patients. The side effects of cannabinoids (eg ataxia, concentration difficulties) are less life threatening in the acute postoperative period. In this situation morphine is the only alternative, again with serious side effects of respiratory depression and apnoea and control of drug use by DDA regulations. The present lack of choice in analgesic drugs without serious side effects must be considered as part of the evidence to promote clinical trials of cannabis (or its constituents, natural or synthetic) for management of acute and chronic pain.

#### **Memorandum by the Independent Drug Monitoring Unit (IDMU)**

Further to previous correspondence, including your letter of 6 May inviting further details of specific evidence from our surveys. I enclose our formal submission to the committee for consideration. I apologise for the delay in submitting the final document, but, as you can appreciate, it has required a substantial amount of new research, which was delayed due to analytical software deficiencies, now resolved, as well as the pressure of day to day casework and research.

The document is not comprehensive, we have not covered in detail the evidence proving the dangers or safety of cannabis, as these matters have been adequately reviewed elsewhere. The review of research into different medical conditions is not complete, as we have yet to be instructed in criminal cases involving particularly glaucoma, MS or appetite stimulation. The existing reviews have originated from reports provided to the criminal courts.

Fortunately, the delay has allowed some consideration of the evidence of previous witnesses appearing before the committee and the questions of members. I particularly hope that in section 8 of the report, we can inform members as to the present treatment of medicinal cannabis cases by UK courts from analysis of our own records/surveys and press reports.

We have not gone into detail over policy recommendations, as in our view the "how" question is as important as "whether or not". If members were minded to relax the prohibition on medicinal use without permitting or encouraging wider recreational use, the situation would be eased by rescheduling of cannabis to allow prescription and improved research, and/or firm guidelines or directives to the CPS on criteria to use when deciding whether a prosecution of a medicinal cannabis user is in the public interest. The California experience (section 7) offers one model for a "medicinal only" policy.

It is important to recognise that many patients, particularly those with severe pain, are currently self-medicating with natural cannabis products and facing criminal penalties as a result. These individuals are unlikely to desist from smoking cannabis while clinical trials are conducted pending licensing of new medicines, and may continue with a preference for the crude product even if other preparations are legally available.

*Matthew J Atha* BSc MSc MEWI  
Principal Consultant

23 July 1998

The Independent Drug Monitoring Unit (IDMU) is an independent research consultancy conducting original research, including large-scale surveys of drug users, and providing expert evidence to the courts in criminal cases involving controlled drugs. We seek to provide independent and impartial advice and information on issues surrounding illegal drugs to all parties within the debate on drugs policy.

The main service provided by IDMU is expert evidence to the criminal courts on most aspects of drug misuse, including comment on consumption patterns, valuations, effects, paraphernalia and yields of cannabis cultivation systems. This is based on existing published studies and our own independent research projects.

IDMU is a commercial organisation not currently receiving any official or charitable funding. Research is currently funded as research/development expenditure paid for by fees derived from legal consultancy activities.

Matthew Atha (BSc MSc MEWI) is the proprietor/director and principal consultant with IDMU, with 16 years experience of research into cannabis consumption and drug policy.

This document has been prepared with the assistance of Sean Blanchard, an independent drugs researcher who is also co-author of Regular Users and other IDMU surveys, and Benjamin Ganley, freelance journalist.

### *Declaration of Interest*

The majority of income of the Independent Drug Monitoring Unit is currently derived from consultancy in respect of criminal prosecutions of drug users, particularly cannabis offenders. Any relaxation in the policy of cannabis prohibition would have adverse implications for our future viability as a business.

## TABLE OF CONTENTS

### SECTION 1—INTRODUCTION

- 1.1 Terms of reference
- 1.2 Comment/sources for specific questions of committee
- 1.3 General questions of committee—a case for change?

### SECTION 2—TYPES OF CANNABIS AND METHODS OF USE

- 2.1 Cannabis Resin
- 2.2 Herbal Cannabis
- 2.3 Cannabis Oil

### SECTION 3—CONSUMPTION PATTERNS OF CANNABIS USERS

- 3.1 UK data
- 3.2 World data
- 3.3 Composition of “joints”
- 3.4 Eating and drinking cannabis
- 3.5 Summary of consumption statistics
  - Table 1: Cannabis use percentiles & THC dosage

### SECTION 4—METHODS OF CANNABIS INGESTION

- 4.1 Routes of administration
- 4.2 Smoking
- 4.3 Oral use and dosages

### SECTION 5—EFFECTS OF CANNABIS—NEW RESULTS FROM IDMU SURVEYS

- 5.1 Effects of duration of use
- 5.2 Cannabis dependence
- 5.3 Note on Driving
  - Table 2: Effects of duration of cannabis use on patterns of use
- 5.4 Reported health problems and benefits—significant associations
  - Table 3: Reported health problems
  - Table 4: Reported health benefits
  - Table 5: Reasons for using cannabis

### SECTION 6—MEDICINAL USES OF CANNABIS—SELECTED LITERATURE REVIEWS

- 6.1 General observations
- 6.2 Medicinal uses
- 6.3 Historical and cultural uses
- 6.4 Cannabis and pain relief



- 6.5 Antiepileptic/Anticonvulsant effects
- 6.6 Cannabis & Stress Relief/Relaxation
- 6.7 Depression
- 6.8 Treatment of Asthma
- 6.9 Cannabis and Opiate withdrawal
- 6.10 Treatment of alcoholism

## SECTION 7—LEGALISING MEDICAL CANNABIS USE—THE CALIFORNIAN EXPERIENCE

- 7.1 Brief history of reform
- 7.2 US Government and Medical Marijuana
- 7.3 Distribution—cannabis buyers clubs
- 7.4 Problems and benefits of Californian system

## SECTION 8—CURRENT TREATMENT OF MEDICINAL CANNABIS USERS BY THE UK CRIMINAL JUSTICE SYSTEM

- 8.1 Overview
- 8.2 Outcomes of arrests of medicinal users (IDMU surveys)
  - Table 6: Outcomes of cases from surveys
- 8.3 Outcomes of criminal cases (IDMU case records)
  - Table 7.1: Medical conditions encountered in referrals
  - Table 7.2: Disposal of cases
  - Table 7.3: Sentencing
- 8.4 Press and internet reports
- References (*not printed*)

## SECTION 1. INTRODUCTION

### 1.1 *Terms of reference*

Your Sub-Committee has invited evidence on the medical use of cannabis and its derivatives. In this report we have attempted to respond to some of your specific questions with data from our own research, and in some cases reviews of the relevant literature where this has been gathered (where IDMU evidence has been provided for legal cases involving medical uses). Some references are given which were not in the BMA report on Therapeutic Uses of Cannabis (November 1997)—chiefly on traditional medical uses and other studies conducted prior to 1970. There are also other sources which may not have been previously brought to your attention. These reviews are not comprehensive, and do not cover important areas including multiple sclerosis, use as antiemetic/appetite stimulant eg in cancer chemotherapy and HIV, or reduction of intraocular pressure in glaucoma sufferers.

In order to reply coherently, we have begun with background information, based on our research and others', which gives the context in which your specific questions can be addressed. This is in: Section 1: Types of cannabis available, Section 2: Methods of use, Section 3: Consumption patterns of regular users, and Tables 1: Amounts smoked per day and 2: Cannabis use levels (percentiles).

Other areas which are relevant though not specifically requested are:

#### *Section 7: Medical use in California*

Briefly describes a recent social experiment in making cannabis widely available for medical purposes, with popular support, legal and medical controls on misuse, and nascent system for production and distribution. Whatever the scientific or other evidence on which they based their vote, Californians devised a system which supports medical uses while maintaining prohibition on recreational use.

#### *Section 8: Treatment of "medicinal" cannabis users by the UK criminal justice system:*

Your Lordships expressed an interest in this matter in a recent session. Data from our research, court experiences, and other sources.

#### *Table 6: Outcomes of criminal prosecutions reported among medicinal users*

#### *Table 7: IDMU Medicinal Cannabis Cases*

## 1.2 Specific Questions posed by the Committee

*What are the physiological effects (immediate, long-term and cumulative), of taking cannabis, in its various forms?*

*What are the psychological effects?*

*Section 5: Effects of cannabis—effects of duration, dependence?, on driving.*

*Section 5.4: Health problems and benefits attributed to cannabis use.*

*Table 3: Reported health problems attributed to cannabis use.*

*Table 4: Reported health benefits attributed to cannabis use.*

*Table 5: Reasons for using cannabis.*

Responses from our surveys of regular cannabis users—total 2,794 respondents. Overwhelmingly the most common positive psychological effect reported by regular users is relaxation/stress relief, followed by mood elevation and increased sociability or personal development. Negative effects most commonly reported include memory problems, paranoia/anxiety, amotivation and respiratory problems. Significant associations between respondents reporting problems, levels of use, and related variables including duration of use, other drug use, spending, subjective ratings of drugs, methods of use etc are summarised in the tables. The most common “beneficial” physical effects are on pain relief and respiratory benefits, such as reduced asthma and drying of mucosae during colds and flu.

*How do these effects vary with particular methods of preparation and administration?*

*Section 4: Methods of Ingestion.* In our studies, an estimated 96.2 per cent of cannabis use is by smoking, usually with tobacco, although 25 per cent of respondents eat or drink it on occasions. Also, a small US study comparing the harmfulness of smoking methods is reviewed.

Smoked cannabis poses clear risks to physical health, as would smoking any substance, although this represents a rapid and controllable route of administration. The effects of oral cannabis preparations vary considerably, with risk of overdose due to the slow onset of action. Many medicinal users report the effects of smoked cannabis to be more beneficial than oral cannabinoids, and it is possible that modulation of the effects of THC by “minor” cannabinoids may reduce some of the unwanted side-effects or potentiate the therapeutic effect.

Our research provides the most comprehensive studies currently available of the dosages of cannabis/cannabinoids and methods of use among large samples of short and long-term cannabis users in the UK.

*To what extent is cannabis addictive?*

*To what extent do users develop tolerance to cannabis?*

*Section 5.1: Effects of duration of use.*

*Table 2: Effects of duration of use on patterns of use.*

A substantial proportion of users continue into middle age, and a greater proportion use the drug daily than with other controlled drugs. After approximately two years experimental and heavy use, average monthly use declines with age. The pattern of cannabis use among regular/long-term users is comparable to that of caffeine, with the average regular user consuming the drug on around five to six occasions per day.

*What is the evidence that cannabis in its various forms has valuable medicinal actions?*

*In the treatment of which diseases?*

*How rigorous is the evidence?*

*Section 6: Medical uses of cannabis.* Raw material versus cannabinoid compounds. Literature reviews on historical uses, pain relief, anti-convulsant, stress and depression, asthma relief, opiate/alcohol dependence.

*Table 4: Reported health benefits attributed to cannabis use.*

There is strong evidence that cannabinoids may be of benefit in the management of pain and spasticity in conditions such as spinal injury, arthritis and multiple sclerosis. Cannabinoids (Nabilone/Dronabinol) have been approved for medical use in treating the side-effects of cancer chemotherapy, as antiemetics and appetite stimulants. There is convincing evidence of bronchiodilator activity, although smoking as a route of administration would not be a preferred route for asthmatics. There is conflicting evidence of the efficacy of cannabinoids in the treatment of glaucoma, epilepsy (particularly cannabidiol), and addiction to opiates and alcohol. Anecdotal evidence of anti-anxiety activity runs counter to the little scientific evidence available, although this may be attributable to differences in the effect of cannabis on naïve and experienced users.



### 1.3 *General questions of the Committee—A Case for Change?*

*Is there a case for promoting clinical trials even if the current level of control is maintained?*

Yes. There is substantial anecdotal evidence of health benefits from cannabis, and from some cannabinoids. Recent work on cannabinoid receptors suggests new lines of enquiry and provides a theoretical basis for several commonly-reported conditions. The Misuse of Drugs Act and other regulations were intended to permit research, but the present licensing system and policy has severely limited research opportunities, and should be reviewed. There is an urgent need for fundamental research and/or clinical trials for a variety of conditions. The risks of morbidity and mortality attributed to cannabinoids are surprisingly low, particularly in comparison to existing medications such as opiates, non-steroidal analgesics and benzodiazepines.

New research is now being published at an increasing rate, recent publications have indicated therapeutic potential of CBD as an antioxidant in the management of strokes<sup>1</sup>, and reduction of tumours in breast cancer from anandamide<sup>2</sup>, and also shown that cannabinoid receptors in the skin are activated by traumatic injury<sup>3</sup>. On the other hand, researchers have also reported gene mutation from cannabis smoke<sup>4</sup>, and a review of cognitive effects in long term users concluded that cannabis may interfere with the “filter” system used by the brain to keep out unwanted or irrelevant information<sup>5</sup>. Clearly the field of “therapeutic” cannabis and cannabinoid research is advancing rapidly, with economic implications from the development of a new class of drugs. Should the UK maintain the hitherto strict regulatory regime, the loss of opportunities for the British pharmaceutical industry to benefit from new product development could damage our international competitiveness.

*How strong is the scientific evidence in favour of permitting medical use?*

In some cases cannabis products may be more effective than other treatments. It would seem inhumane to completely block legal access to a substance which makes sick people feel better, when no better alternative is available, even if any beneficial effects were of unknown aetiology or of undetermined efficacy. Where the drug is of demonstrable benefit and alternative treatments are less effective or carry greater risks, a continued refusal to permit medicinal use, due to perceived risks of a change in public attitudes, appears unjustifiable both on moral and on public health grounds.

*How strong is the scientific evidence in favour of maintaining prohibition of recreational use?*

Some commentators would seriously argue that legalising the recreational use of cannabis would lead to a breakdown of society, others would counter that cannabis/hemp could “save the world”. In our view, both these positions are equally erroneous.

The potential harmful effects of cannabis have, over the past century, been investigated far more thoroughly than potential benefits, with generally negative results. The main physical dangers associated with cannabis arise from smoking it, particularly mixed with tobacco in unfiltered cigarettes, leading to respiratory or cardiovascular problems. Psychological risks include anxiety/panic/paranoia attacks mainly among naïve users, and a risk of psychosis in a small number of predisposed individuals. Even if the worst plausible dangers were all proved, using cannabis would pose a lesser risk to health than many common sports, other recreational activities, legal drugs or products such as alcohol, tobacco, caffeine, sugar or saturated fats.

Governmental and medical reports, from several countries including the UK, have suggested that the harmful effects of a prohibition policy, on individuals and society, may be greater than the harmful effects of the drug. Prohibition, particularly the effects of arrest, may reinforce rather than deter drug use by reducing the options for full participation in society, including lost opportunities for employment, housing, foreign travel and to the user’s driving licence as a result of a criminal record or positive urine sample.

Prohibition has created a confrontational atmosphere which stifles open debate and dissemination of information as to the real risks of using different drugs, and creates an incentive to experiment among teenagers keen to rebel against the strictures of their elders. A forbidden fruit, when no longer forbidden, loses much of its sweetness. Experience in the Netherlands and elsewhere does not suggest that a relaxation in the law leads to an increase of use over the longer term, and rates of drug use, including problem indicators, in Holland are lower than in the UK.

Scientific evidence is only one of a number of considerations which apply in formulating drug policy; public moral and political attitudes and international treaty obligations appear to take precedence over rational consideration of such evidence. Any decision as to the desirability and nature of law reform would need to take account of matters beyond the scope of this committee, including prevalence of use, effects on crime/driving, economic effects both direct (enforcement expenditure, tax revenues) and indirect (effect on manufacturing industry and employment of reduced acquisitive crime), international relations (including drug tourism) and social attitudes, as well as public health considerations and the proper constitutional role of the state in the control of individual behaviour.

The nature of any change in the law is critical, whether this involves an increase or reduction in penalties, rescheduling to Class C (de facto decriminalisation of possession), and/or the means of achieving a legitimate

method of supply in a legalised market (eg taxation/regulation, licensing, coffee-shops, clubs or free-market solutions). Each of these options would create advantages and disadvantages which must be carefully weighed before any policy is adopted.

## SECTION 2. TYPES OF CANNABIS AVAILABLE ON THE ILLICIT MARKET IN THE UK

### 2.1 *Cannabis resin*

2.1.1 The most common form of cannabis resin is of Moroccan/North African origin, also known as “soap-bar” with a THC content typically between 4 and 7 per cent. The resin appears in the UK in compressed bars, normally 250 grams/9 ounces.

2.1.2 The second most common form of resin is of Asian origin, being darker in colour and of soft, pliable consistency. Mostly from Pakistan or Afghanistan, it often appears in 1 kilogram blocks wrapped in red cellophane. THC contents typically 4 per cent to 10 per cent, may also contain perfume agents such as caryophylline.

2.1.3 Other types of cannabis resin appear occasionally. Lebanese resin was the “Market Leader” in the 1980s but is now rarely seen. Occasionally more exotic Himalayan varieties, with THC contents in the region of 10 per cent, appear in small quantities.

2.1.4 In the Netherlands, coffee-shops supply a wide variety of cannabis resins and herbal cannabis, with prices linked to quality (ie lower qualities provide larger fixed-price “deals”). The Netherlands has also started producing resin from domestically-produced crops. I know of one instance in the UK where resin produced from exceptional plants has approached a THC content of 60 per cent.

2.1.5 The overall quality of imported cannabis and cannabis resin appears to have fallen in recent years, many users perceive cannabis resin as adulterated, and forensic analysis has discovered common contamination of resin of both major types with “caryophylline” a constituent of cloves, also used in the perfume industry.

### 2.2 *Herbal Cannabis*

2.2.1 Until recently, most herbal cannabis in the UK was imported from Africa, the Far East and Caribbean, however home-produced cannabis may now represent the major source.

2.2.2 Imported cannabis appears in compressed blocks normally bearing seeds, and would typically have a THC content of 3–8 per cent. Such material frequently appears in poor condition with mould and decomposition present (accelerated if damp—potential risk for immuno-compromised individuals).

2.2.2 Home grown herbal cannabis falls into three basic categories. “Hemp” is the fibre-producing variety which can be cultivated under licence for industrial uses, and would normally produce a THC content of under 0.5 per cent (although some long-established cultivars, and individual plants, may produce higher or lower THC contents), and a relatively high CBD:THC ratio.

2.2.2 Until recent years, most domestically produced cannabis for drug content was derived from seeds in imported “deals”. THC content would be from 1 per cent to 8 per cent, similar to imported cannabis.

2.2.3 In the past decade, commercial seed developers based in the Netherlands have developed a number of cultivars (eg “Skunk”, “Northern Lights” and many others) suited for indoor growth by virtue of short stature (internodal lengths), and early flowering. THC contents are increased by preventing pollination of female plants by males, leading to “sinsemilla”—development of extensive flowering tops. The THC contents of these varieties in ideal conditions vary considerably, from around 5 per cent to 15 per cent, with exceptional cases producing 20 per cent THC. The cannabinoid spectrum of these plants also varies. I am not aware of any data available on the actual cannabinoid composition of different varieties, although CBD levels tend to be low or absent.

2.2.4 The THC contents associated with “Skunk” cannabis should not be considered unusual, as similar potencies were reported from some imported material seized in the 1970s and 1980s. Furthermore, THC losses in storage and transportation can render imported cannabis significantly inferior to domestically-produced product.

### 2.3 *Cannabis Oil*

2.3.1 The legal position of liquid cannabis (also known as “hash oil”) is currently the subject of legal argument. This dark, viscous, liquid is prepared from solvent extraction of cannabis plants, and contains a high level of THC (10 per cent to 70 per cent).



## SECTION 3. CONSUMPTION PATTERNS OF REGULAR CANNABIS USERS

## 3.1 UK data

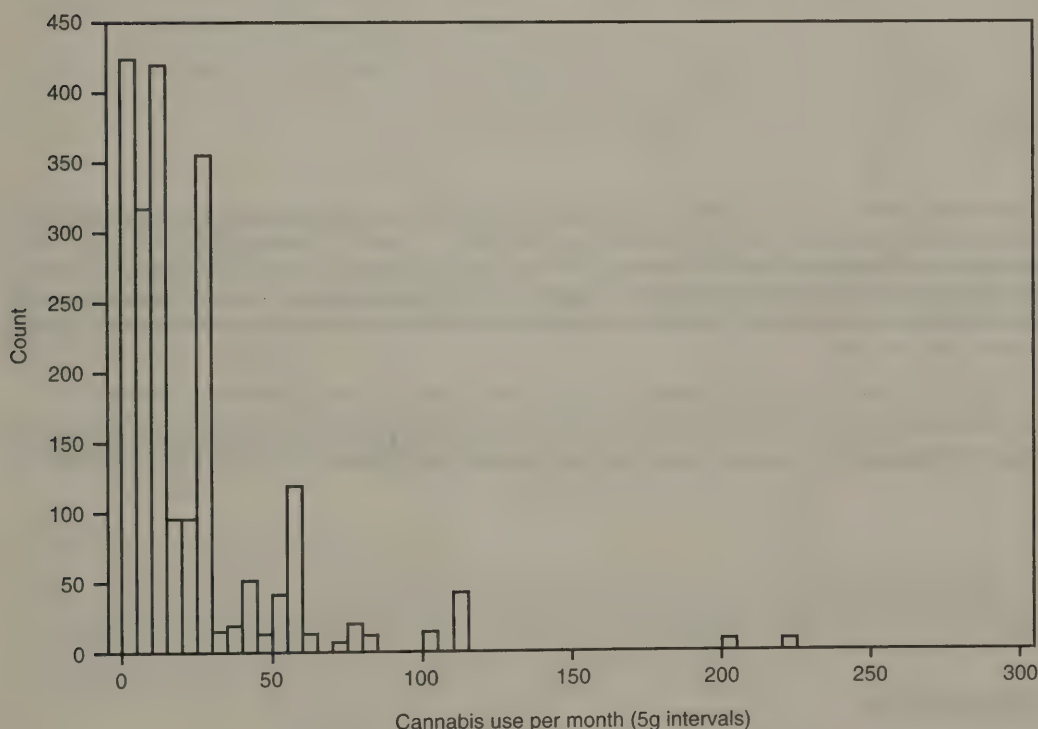
3.1.1 Our research into cannabis consumption<sup>6 7</sup> was originally based on two surveys (1982 and 1984) of self-selected regular cannabis users, finding that the “average” (mean) cannabis usage was just over one ounce per month (29.3–29.9g). Both surveys showed very similar patterns, with a large number of relatively moderate users (median usage was 14g/month), but a smaller number of heavy and very heavy users (mean use for “more than daily” users was 65.8g), with the maximum usage of 150g, or just over 6 ounces, per month. Users of imported herbal cannabis had a higher mean consumption (57.1g/month) than users of resin.

3.1.2 Results from “Regular Users”, our 1994 survey of cannabis consumption<sup>8</sup>, using data collected from 1,333 drug users, from a UK pop festival in June 1994, and further samples distributed by direct mail and by snowballing, suggested very little difference from the 1984 figures. The overall mean monthly cannabis consumption of the respondents was 24.8g per month.

3.1.3 Consumption of cannabis by daily users averaged 34.8g per month, with mean purchase of 60.1g per month. These daily users averaged 7.7 “spliffs” per day, as against the overall average of 5.98 per day. The maximum accepted personal consumption (10 respondents) was 200–150g, or 7–9 oz per month.

3.1.4 The 1994 and 1997 survey samples both showed similar mean cannabis usage (overall 24.8g, 23.92g respectively) and distributions, and were combined to form a total sample of 2,469 users. The distribution of monthly consumption (fig 1) is shown below.

**Figure 1**  
**Distribution of monthly cannabis use**



3.1.5. As with our previous studies, the majority of cannabis users consume relatively modest amounts, although there are a minority of heavy users who consume substantially more than “average”. The top credible consumption was 400g or approximately ½oz per day, by a grower who had produced 208 plants in his most recent crop. At 3–15 per cent THC, this could represent between 400mg and 2000mg THC per day. He reported “memory loss” as a health problem and did not report any health benefits! There was a small cluster of 19 respondents in the range 200–250g (approx 2oz per week), representing THC intakes of between 200mg and 1,250mg per day. This contrasts with the maximum reported cannabis use in the literature of 10g/day (McBride)<sup>9</sup> in the UK, and 50g per day (Schaeffer et al)<sup>10</sup> in the Caribbean (estimated at 4,000mg THC/day based on determined 8 per cent THC content).

3.1.6 Fairbairn’s 1973 study of reefer content<sup>11</sup> quoted regular use by three groups of experimental subjects of (a) 2g to 6g of cannabis per day (mean 3.8g), (b) 0.1g to 1g per day (mean 0.3g), (c) 0.3g to 8.3g per day (mean 2.8g), some users smoking 10–20 reefers per day. The heaviest user in this study would have consumed 252g per month, consistent with the heaviest reported use from our surveys.

3.1.7 Caplin & Woodward<sup>12</sup>, for the BBC's Drugwatch TV special, conducted a survey of drug users in 1984. The "cannabis only" users spent an average £12 per week, representing 3.8g to 5.9g per week at 1984 prices<sup>13</sup>. The heaviest 8 per cent, spending up to £30 per week, would have used 9.6g to 15.8g per week at 1984 prices. However, these did not include the "cannabis plus" (other drugs) users, who spent up to £200 per week in total. The Drugwatch study can be criticised on a number of grounds, as it asked viewers to write in for a detailed questionnaire following graphic portrayals of the problems associated with hard drug use. The overall response rate is not stated (3,000 questionnaires were distributed) although the "cannabis only" group constituted only 3 per cent of the total sample.

3.1.9 McBride's recent study of cannabis use in 100 attenders at a drug and alcoholic clinic in South Wales<sup>14</sup>, found average cannabis use of 10.5g per week (approx 45g per month) with the heaviest user reporting 70g per week at a cost of £250. McBride calculated, on the basis of responses to questions about the number of joints per "eighth" or "sixteenth", that users would consume 350mg of cannabis resin, or 620mg herbal cannabis, in a joint. Those who did not use tobacco consumed about 27 per cent more cannabis or resin per cigarette or pipe than those who used a mix, although there was no difference in the overall cannabis usage between these two groups.

3.1.10 Approximately 2–5 per cent of regular cannabis users purchase the drug on a "less than monthly" basis<sup>15</sup>, buying several ounces at a time to take account of bulk prices. The average quantity purchased per transaction increases sharply with the duration of use (particularly among users of over 20 years standing), and the proportion reported to be used personally is also highest amongst this age group.

### 3.2 *World data*

3.2.1 In countries where use of cannabis is traditional, and where plentiful supplies are cultivated locally, the amount consumed can exceed 2oz (56g) per day, eg Schaeffer<sup>16</sup>, Carter<sup>17</sup>. Looking at the dosage of THC to which smokers were exposed, Rubin<sup>18</sup>, Bowman & Pihl<sup>19</sup>, and Beaubrun<sup>20</sup> found THC dosages of 60 to 420 mg/day, equivalent to smoking 4 to 28 grams ( $\frac{1}{8}$ oz to 1oz) of cannabis per day with 3 per cent THC (allowing for wastage during smoking). Stephanis et alia<sup>21</sup> found that hashish users in Greece used an average of 7.48g (approx  $\frac{1}{4}$ oz) per day.

3.2.2 To put these figures into perspective, a person who smokes 30 cigarettes per day will consume roughly 1 ounce (28g) of tobacco per day, as each filter cigarette contains approximately 800mg–1.0g of tobacco.

### 3.3 *Composition of "Joints"*

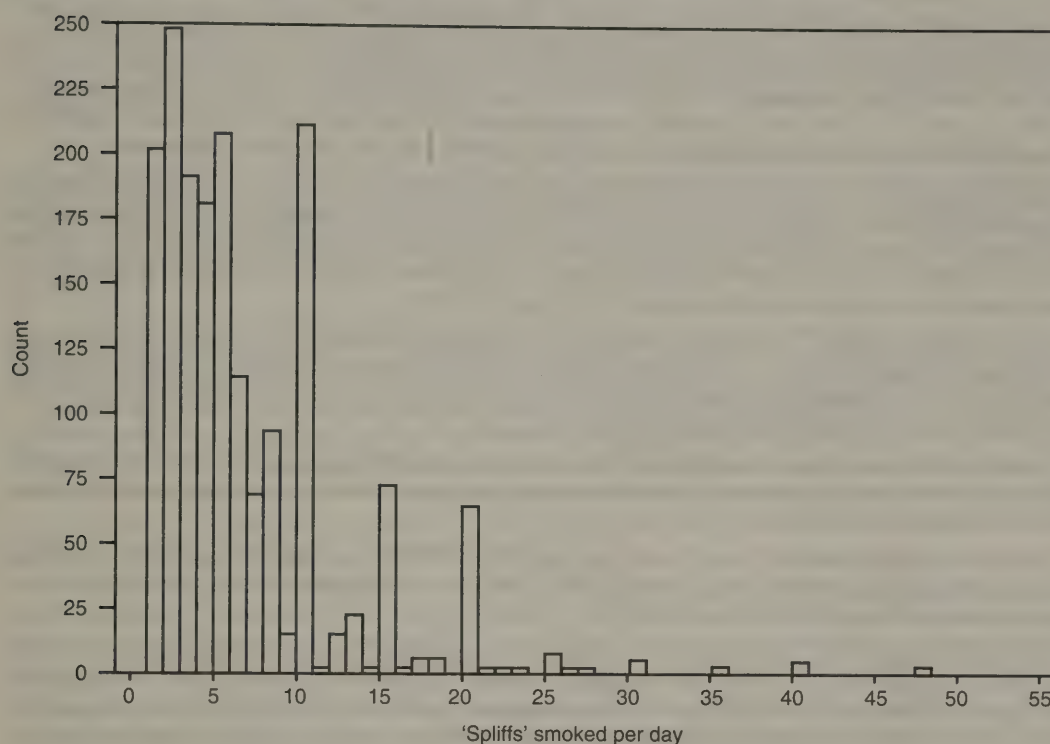
3.3.1 Published<sup>22</sup> and unpublished Home Office data<sup>23</sup> suggests that the average (mean) amount of cannabis (normally mixed with tobacco) in what they call a "reefer" cigarette is approximately 200mg. However, a crude average can represent either a broad or a narrow distribution of results. These, and other reports<sup>24</sup> have shown a very wide range of amounts of cannabis in a "joint", from a few milligrams to over one gram with virtually all reports showing a significant minority of cigarettes containing over 300mg of cannabis. The main criticism of these reports is that they have only analysed cannabis reefers rolled with tobacco. Very few complete unsmoked reefers rolled with "home grown" appear in the samples.

3.3.2 Results from our 1994 survey<sup>25</sup> give similar distributions. By dividing the reported monthly cannabis use by the total number of pipes and reefers smoked, it was possible to arrive at a crude estimate of the amounts of cannabis in reefers. The mean amount was 155mg, with 10.6 per cent of the estimates being over 300mg, 3.3 per cent over 500mg, and 1.7 per cent over 750mg.



3.3.3 From the combined 1994–97 surveys, the distribution of number of “spliffs” (reefers) smoked per day are shown in figure 2 below.

**Figure 2**  
**Distribution of number of ‘spliffs’ smoked per day**



### 3.4 Eating and Drinking Cannabis

3.4.1 Around 1 to 2 per cent of users consume 50 per cent or more of their cannabis in food or drink, and around 25 per cent eat or drink their cannabis on occasions<sup>26</sup>. Consumption of cannabis in a tea is increasingly common, particularly among non-smokers seeking a medicinal benefit, and in West Indian (Ganja tea) and Asian communities (bhang).

3.4.2 Recipes for cannabis typically call for up to half an ounce or more of cannabis leaves<sup>27</sup>, which can also be used as a salad vegetable. Cannabis tea is likely to require 2–3 grams of leaves per cup—a Brooke Bond tea bag contains just over 3 grams of tea<sup>28</sup>.

### 3.5 Summary of consumption statistics

3.5.1 The equivalent consumption levels and “reefers per day” of users at different percentiles of the above range is as shown in table 1 below. The top 4 per cent would use 1 ounce per week or more (one user in 25), 1 per cent would smoke 200–250g per month. The most commonly reported use was 28g, or one ounce per month, although median usage was equivalent to one eighth ounce per week.

**Table 1**  
**CANNABIS USE PERCENTILES**  
(1994–97—n = 2469)

| Percentile     | Monthly use | Weekly use | Daily use | THC @ 3% | THC @ 15% | Joints per day |
|----------------|-------------|------------|-----------|----------|-----------|----------------|
| 50% (median)   | 14g         | 3.5g       | 0.5g      | 15mg     | 75mg      | 5              |
| Top 25% (mode) | 28g         | 7g         | 1g        | 30mg     | 150mg     | 10             |
| Top 10%        | 56g         | 14g        | 2g        | 60mg     | 300mg     | 15             |
| Top 5%         | 76g         | 19g        | 2.7g      | 81mg     | 405mg     | 17             |
| Top 1%         | 200g        | 50g        | 7.1g      | 213mg    | 1065mg    | 23             |
| Maximum        | 400g        | 100g       | 13.3g     | 400mg    | 2000mg    | 47             |

## SECTION 4. METHODS OF CANNABIS INGESTION

### 4.1 *Routes of administration*

4.1.1 Most cannabis in the UK is consumed in hand-rolled cigarettes (“joints”, “reefers” or “spliffs”) combined with tobacco, accounting for over 70 per cent of consumption<sup>29 30</sup>. Herbal cannabis is frequently smoked without added tobacco, accounting for about 5 per cent of consumption, or smoked in pipes (16 per cent). Either herbal cannabis or resin may be eaten by itself or in other food (4 per cent). (By contrast, the most common form of marijuana consumption in the USA is the neat rolled cigarette.) Cannabis resin accounts for around 60 per cent of the total used, imported cannabis around 10 per cent, and domestically-produced cannabis around 30 per cent. Cannabis oil accounts for a small fraction of 1 per cent of the market.

4.1.2 Cannabis can be smoked with or without tobacco in a pipe or water pipe (“bong”). Other methods of smoking without tobacco include “hot knives” where a piece is crushed between red-hot blades and the vapours inhaled, or a coal is left to smoulder and the smoke collected in a glass, bottle or bucket before inhalation. Although smoking around two to six pipes per day would represent average consumption, a significant minority of users will consume in excess of 15 pipes per day.

4.1.3 Cannabis resin “joints” with tobacco contain on average approximately 150mg, resin, range around 50mg to 350mg. Herbal cannabis “joints” with tobacco contain an average of around 200mg cannabis, although amounts vary considerably. A minority of herbal cannabis users, mainly those who grow their own, smoke cannabis in neat cigarettes containing 500mg to 1g.

4.1.4 Cannabis Oil when smoked is commonly smeared on to a cigarette paper and tobacco then enclosed, or a drop is mixed with tobacco before the material is rolled in the paper. As it is inconvenient to smoke, many users of oil prefer to use it in cooking.

4.1.5 Use in oral preparations is limited by the lipid solubility of THC and other cannabinoids, requiring use of fats or alcohol to emulsify the drug into an edible form. The main problem is the risk of overdose, as the effects are slow to develop but can be intense.

4.1.6 The BMA report<sup>31</sup> on therapeutic uses referred to particulate studies of cannabis and tobacco cigarettes, originally published in 1982 by the National Institute on Drug Abuse in the USA. The cannabis used was of poor quality by today’s standards (approximately 1 per cent THC). It is by no means clear whether the composition of smoke from high potency cannabis would be similar to the cannabis used for that study, and I am unaware of any studies as to the content of smoke arising from cannabis resin in pipes or resin/tobacco reefers. Such research should be considered a priority.

4.1.7 A recent study of water pipes and other smoking paraphernalia found that an unfiltered pure cannabis cigarette was as effective a method of delivery as any of the devices tested, using criteria of THC dose to particulates and other potential carcinogens. However, one of the vapourisers tested did perform similarly. Most water pipes absorbed too much THC, leading the user to smoke more to achieve the desired “high”.

### 4.2 *Smoking*

4.2.1 Methods of ingestion vary widely in prevalence across the globe. 77.6 per cent of cannabis use in the UK is by smoking joints, the majority of which contain tobacco. Smoking in all its forms accounted for some 96.2 per cent of our samples of methods.<sup>32</sup>

4.2.2 Whether cannabis smoke is more or less harmful than tobacco smoke is an argument that constantly rages between the extremes of the drug debate. It is however, irrelevant, as all research indicates that both substances contain a variety of carcinogens such as polycyclic aromatic hydrocarbons as well as other noxious substances.

4.2.3 The preference for smoking as a method of ingestion may be a result of several different factors. Smoking cannabis produces noticeable effects far more immediately than when it is eaten or drunk. It is also consumed in small, discrete amounts over a mildly extended period of time. The dosage is easily controlled by self-titration. In contrast eating cannabis, whether raw or in preparations, predicates towards consuming the entire uncertain dosage at once. This can easily result in consumption of less or more than required to achieve the desired effects.

4.2.4 Traditionally cannabis users have viewed the health risk of each method of ingestion to run from greatest to least in the following order: joint with tobacco, neat joint, pipe, water pipe, vaporiser and eaten. This has been based on observable differences in each method and on “common sense”.

4.2.5 In a joint the entire matter is inhaled leaving very little residue other than a fine ash. This indicates that the user is ingesting all the compounds from the drug as well as those from the paper and tobacco. The smoke inhaled is of a reasonably high temperature, which increases as the joint is consumed and the cooling effect of the journey from tip to mouth is reduced.

4.2.6 Smoking cannabis in pipes immediately removes tobacco compounds, as well as those contained in the paper. A proportion of the tars and oils remain fixed to the inner surfaces of the pipe.



4.2.7 Water pipes have several advantages over other forms of smoking since a percentage of the tars and particulate matter are retained in suspension as the vapour passes through the reservoir, as well as on the inner surfaces of the pipe. Fairbairn's group postulated<sup>33</sup> that, since the natural inhibitor of THC action which is present in cannabis is water soluble, the use of water pipes will reduce its effects and in consequence maximise the psychoactive effect.

4.2.8 More recently the UK and US cannabis scenes have witnessed a growth in popularity of the vaporiser. Vaporisers are designed to heat the drug to the point at which the volatile cannabinoids are released without the plant material combusting. The desired result is to maximise the cannabinoids ingested without necessarily inhaling the particulates and tars.

4.2.9 Recent harm reduction research in America<sup>34</sup> has thrown doubt on the traditional beliefs concerning the health risks associated with the various forms of inhalation. Seven devices (a filtered joint, an unfiltered joint, a portable water pipe, a traditional bong, a battery operated water pipe, a vaporiser and a hybrid water pipe/vaporiser) were tested, and the amounts of cannabinoids and solid particulates delivered to the user were measured and compared. In all cases the devices used neat marijuana supplied by NIDA with a potency of 2.3 per cent THC.

4.2.10 The researchers were surprised to discover that the water pipes were consistently outperformed by the unfiltered joint (with a ratio of 1 part cannabinoids to 13 parts tar). The best performing water pipe was matched by the filtered joint, both devices producing about 30 per cent more tar per cannabinoids. The two vaporisers did better than the unfiltered joint, although the hybrid device only just so, while the pure vaporiser outperformed the joint by some 25 per cent. However, the vaporiser produced much lower levels of THC and higher levels of non-psychoactive CBN than the other devices. While this might not be a problem for users whose primary purpose is medicinal the study was intended to aid harm reduction in recreational users, and so results were recomputed to provide a THC to particulates ratio. When this was done the pure vaporiser fell to a position below that of the unfiltered joint.

4.2.11 The researchers point out that no reading of the noxious gases produced in the burning of marijuana were measured. Gases such as hydrogen cyanide, volatile phenols, aldehydes and carbon monoxide are known to occur. Since water filtration has previously been shown to be effective at removing some of them, the team conducted that further research may indicate that the use of water pipes may offer a net health benefit.

4.2.12 In addition, THC transfer rates were computed to establish the smoking efficiency of the various devices. Again, the unfiltered joint performed surprisingly well and, along with the bong and the portable water pipe, delivered about 20 per cent of the THC to the user. All the other devices had transfer rates less than one third as efficient as the top three devices.

4.2.13 The research was carried out in terms of harm reduction, with a view to reducing the amount of carcinogenic tars inhaled rather than non-carcinogenic cannabinoids. In consequence, the researchers reached the conclusion that the higher the ratio of THC to tars the better, since users normally regulated their doses based on how profound an effect they achieved rather than on the amount of cannabis consumed. Therefore, if a greater degree of "high" were obtained from a smaller amount of cannabis then the amount smoked would decrease proportionally.

4.2.14 This reasoning also leads to the conclusion that the higher the potency of the cannabis smoked the lower the amount smoked. The results were obtained with 2.3 per cent THC cannabis, while commonly available cannabis on the street has higher levels of THC with no increase in tar levels. Had cannabis with a potency of 12–14 per cent THC been used then, the researchers suggested, users would be able to reduce their inhalation of tar by a factor of five while still achieving the desired level of high.

### 4.3 Oral Use and Dosages

4.3.1 When cannabis is taken orally, the effects take much longer to develop and peak (1–2 hours, as opposed to a few seconds), and subside more slowly. THC, not being water-soluble, must be taken with some fat, oil or alcoholic carrier to permit absorption into the blood. It is generally considered that up to three times as much cannabis is required when taken orally compared to smoking the drug, as evidenced by the equivalent analgesic efficacy of THC doses of 20mg taken orally<sup>35</sup> and 7.5mg smoked<sup>36</sup>.

4.3.2 According to Parke-Davis<sup>37</sup> a 70kg man should require 4mg/kg, or 280mg (solid extract) as an effective dose. This would be consistent with approximately one gram of quality cannabis tops (5–10 per cent potency). Animal studies have suggested higher effective doses<sup>38</sup>.

4.3.3 One would expect the user to achieve the most appropriate dose level over time through experience of the desired and the adverse effects. Apart from potentially disturbing psychological effects, the risks to physical health from overdose are not significant.

4.3.4 The BMA have called for further research on appropriate dosage regimens and routes of administration for cannabinoids. Oral preparations, aerosol inhalants, rectal suppositories and skin patches have been discussed.

4.3.5 The economic cost of producing synthetic THC (Dronabinol) is considerably higher than the cost of producing high-potency plants, solvent extraction of the THC and other cannabinoids, and separation via

column chromatography. If licensing of preparations for medicinal use is to be considered, these should not be restricted to synthetic products where natural alternatives of known cannabinoid content can be provided more cheaply.

## SECTION 5. EFFECTS OF CANNABIS—NEW RESULTS FROM IDMU USER SURVEYS

### 5.1 *Effects of duration of use*

5.1.1 The effects of cannabis differ between naïve and experienced users. Naïve users commonly feel either no effect, or alternatively experience intense effects which some find distressing, and which can lead to panic attacks. Many individuals discontinue use at such a point. Experienced users commonly report a sense of relaxation and calm, relief of stress and pain, and enhanced sociability. Tolerance develops both to physical and psychotropic effects, such that the “high” is diminished, but can also be “switched on and off” according to set and setting.

5.1.2 The scientific literature provides conflicting evidence of cognitive and psychomotor impairment. Commonly impairment is most marked in naïve users under acute intoxication, or with high doses arising from over-use of more potent preparations, whereas many daily users smoke relatively high doses without any noticeable effects on performance, even in studies involving very heavy chronic users.

5.1.3 Although the prevalence of cannabis use falls after age 30, the proportions reporting use to the British Crime Survey in the older age groups showed the greatest proportional increase during the period 1991–96<sup>39 40</sup>, with lifetime prevalence doubling in the 40–44 age group (from 15 per cent to 30 per cent, also 8 per cent higher than the 1991 35–39 year old cohort) and trebling (from 3 per cent to 10 per cent) in the 45–59 age group.

5.1.4 The proportions admitting cannabis use within the past year remained relatively stable between the two British Crime Surveys, when successive age cohorts are compared. Thus the relatively low levels of use by the over 30s appear to reflect a generational/cultural effect rather than substantial numbers of users giving up use.

5.1.5 Using the data generated by the IDMU surveys conducted between 1994 and early 1998, we sought to establish whether there is any evidence of increased or decreased levels of cannabis use as a function of the duration of use, and to plot the progression of use over time. Duration of cannabis use was established by subtracting age of first use from current age, and for analyses divided into six categories:

1. Missing values and errors
2. Used 0–1 years
3. Used 2–5 years
4. Used 5–10 years
5. Used 10–20 years
6. Used over 20 years

5.1.6 The typical pattern of use appears to be the “up peak down” model identified by Cohen and Sas<sup>41</sup>, whereby users experiment and use a variety of drugs increasingly heavily during the early part of a drug-using career, but after 5–10 years develop a settled pattern of use involving daily cannabis and occasional use of other drugs. There is little evidence for any further escalation after two years, indeed average monthly cannabis use declines thereafter with age. There is no evidence of increased levels of cannabis use over the longer term.

5.1.7 Differences manifest themselves in purchase patterns; longer-established users tend to buy larger quantities at one time, leaving themselves open to charges of “possession with intent” if arrested, even though a greater proportion of their purchases are intended for personal use. Users of over 20 years standing consume a greater proportion in pipes and eaten, and a lower proportion of tobacco “joints”.

5.1.8 It is clear that a substantial proportion of cannabis users continue to use the drug well into middle-age, and that a greater proportion of cannabis users use the drug daily than with other controlled drugs. The pattern of use is broadly similar to that seen with caffeine, which is used several times per day by most UK citizens, and in many cases for similar reasons (relaxation, mental stimulation). Most users consume relatively small amounts—one gram per day or less, although a small number of very heavy users exist. (See Table 2 below.)

### 5.2 *Cannabis Dependence?*

5.2.1 Recent developments in cannabinoid neurobiology have raised the question of cannabis addiction, on the basis of a common action of dopamine release mediated by  $\mu$ -opioid receptors in the nucleus accumbens<sup>42</sup>. The action of THC and a synthetic cannabinoid were blocked by both cannabinoid antagonist and naloxone, whereas heroin activation of dopamine was blocked by naloxone only. This suggests the action of cannabis/anandamide to take place “upstream” of the opiate/endorphin system, possibly stimulating the release of endogenous opioids or altering receptor activity, which has implications both for the management of pain and for the treatment of addiction to other drugs. A neurochemical basis for cannabis withdrawal



symptoms was also postulated by Fonseca *et al*<sup>43</sup>, based on CRF release in the amygdala produced by administration of a cannabinoid antagonist to rats pre-treated with a potent cannabinoid agonist (many times more potent than THC).

5.2.2 Withdrawal symptoms from cannabis are reported as including irritability, restlessness, disturbed sleep and anxiety, although the reduction in plasma cannabinoid levels following cessation of use is more gradual than with opiates or stimulants.

### 5.3 Effects on driving

5.3.1 Evidence as to the effects on driving ability is inconclusive. While some studies have shown impairment of psychomotor function and procedures involving complex multitasking (eg among airline pilots), moderate doses of cannabis or THC show little or no effect on actual driving performance. Where some impairment in performance is demonstrated, the level of impairment is normally lower than that produced by alcohol intoxication at blood concentrations below present and proposed legal limits. As with other effects, the level of impairment is greatest among naïve users and/or inexperienced drivers.

5.3.2 The evidence from road accident casualties, and from our own surveys, does not lead to a conclusion that cannabis use is a major cause of road accidents, when compared to prevalence levels within the same age cohort. Our own 1994 survey found reported accident rates per 100,000km, among a survey sample mainly under 30 years old, not to be significantly higher than the national average from all drivers. However we do not yet consider this research to be conclusive, and ongoing studies are being undertaken.

Table 2

#### EFFECTS OF DURATION OF CANNABIS USE ON PATTERNS OF USE

| Variable                       | Missing/<br>errors | Used 0–1<br>years | Used 2–5<br>years | Used 5–10<br>years | Used 10–20<br>years | Used over<br>20 years |
|--------------------------------|--------------------|-------------------|-------------------|--------------------|---------------------|-----------------------|
|                                | Mean               | Mean              | Mean              | Mean               | Mean                | Mean                  |
| Count                          | n = 119            | n = 73            | n = 511           | n = 1011           | n = 812             | n = 267               |
| Age***                         | 26.49              | 19.36             | 19.51             | 22.42              | 28.89               | 41.47                 |
| Age first cannabis use***      | 15.90              | 18.53             | 16.37             | 15.73              | 15.64               | 16.29                 |
| Cannabis monthly spending (1)† | 57.53              | 29.51             | 47.61             | 94.78              | 68.80               | 67.18                 |
| Cannabis Rating                | 8.13               | 8.54              | 8.58              | 8.92               | 8.86                | 9.04                  |
| Cannabis amount per purchase*  | 9.75               | 4.96              | 11.36             | 15.19              | 24.29               | 55.60                 |
| Cannabis purchase unit price*  | 29.95              | 17.87             | 36.79             | 48.65              | 67.34               | 80.77                 |
| Average per cent personal use* | 76.74              | 65.68             | 68.09             | 68.51              | 69.16               | 77.36                 |
| Monthly cannabis use(g)        | 33.11              | 12.34             | 29.99             | 25.90              | 24.91               | 23.25                 |
| Monthly cannabis purchase      | 55.35              | 36.13             | 23.92             | 64.37              | 53.82               | 37.33                 |
| Monthly cannabis spending (2)  | 78.22              | 52.47             | 54.23             | 110.9              | 89.16               | 97.93                 |
| Per cent soapbar resin use***  | 47.55              | 47.89             | 36.48             | 36.06              | 42.60               | 45.61                 |
| Per cent “unknown” resin*      | 28.75              | 41.39             | 30.74             | 21.54              | 23.92               | 27.84                 |
| Per cent “Thai bush” use*      | 17.17              | 31.43             | 15.45             | 16.43              | 10.45               | 6.94                  |
| Per cent “Skunk” use**         | 28.94              | 28.27             | 18.19             | 24.08              | 25.72               | 29.65                 |
| Per cent “unknown” bush*       | 20.86              | 32.46             | 29.49             | 21.46              | 20.07               | 17.23                 |
| Per cent use tobacco reefers*  | 64.47              | 72.44             | 72.57             | 73.4               | 72.45               | 63.98                 |
| Per cent use “neat joints”***  | 19.33              | 5.77              | 4.97              | 4.45               | 4.60                | 7.52                  |
| Per cent use water pipe        | 3.60               | 8.56              | 9.53              | 10.13              | 8.18                | 6.64                  |
| Per cent use other pipe        | 4.40               | 5.87              | 6.34              | 5.56               | 7.47                | 10.56                 |
| Total pipes %                  | 8.00               | 14.43             | 15.87             | 15.69              | 15.65               | 17.20                 |
| Per cent eat neat***           | 0.07               | 0.77              | 1.17              | 1.17               | 1.06                | 3.80                  |
| Per cent eat other food        | 1.73               | 3.23              | 2.19              | 1.93               | 2.50                | 3.66                  |
| Per cent drinking              | 0                  | 0                 | 0.19              | 0.11               | 0.08                | 0.71                  |
| Total eat/drink %              | 1.80               | 4.00              | 3.55              | 3.21               | 3.64                | 8.17                  |
| Per cent hot knives***         | 6.40               | 1.82              | 1.24              | 1.32               | 0.61                | 0.72                  |
| Per cent other smoking         | 0                  | 0.10              | 1.20              | 0.83               | 1.70                | 0.73                  |
| Per cent other method          | 0.07               | 1.05              | 0.69              | 0.76               | 0.29                | 0.68                  |
| Error rate %                   | 0.7%               | 1%                | 2%                | 5%                 | 11%                 | 4%                    |
| Reefers per day***             | 4.81               | 2.62              | 4.84              | 6.25               | 6.06                | 5.74                  |
| Pipes per day                  | 1.38               | 0.91              | 1.98              | 2.75               | 2.61                | 2.85                  |
| No. of plants grown            | 12.82              | 2.76              | 19.08             | 13.08              | 27.02               | 30.43                 |
| Per cent busted—cannabis***    | 25.0%              | 4.92%             | 14.2%             | 20.5%              | 34.5%               | 49.4%                 |

Eighty two per cent of respondents answering the “methods” question correctly added up to 100 per cent, eight respondents (0.4 per cent) gave totals in excess of 200 per cent.

#### 5.4 Health Problems and Benefits attributed to cannabis use

5.4.1 IDMU has conducted surveys since 1994 and developed a database (to June 1998) of 2,794 drug users. Questions have included data on drug consumption patterns, attitudes to drugs, driving behaviour and contact with the law or treatment services. All of the users were asked whether they had experienced health problems or benefits as a result of using cannabis, and if so what problems or benefits were reported. The latter were open-ended "write in" questions entered as summaries or quotes. These were subsequently consolidated into a number of different categories, eg "amotivation" included quotes such as "tiredness", "laziness", "missed lecture" etc. These categories were not mutually exclusive, as a proportion of respondents reported a number of problems and/or benefits, and a further proportion stated simply "yes" to the general questions but listed no specific problems and/or benefits. As questions about each effect were not specifically asked, the prevalence of such effects within the user population is likely to be underestimated by these results.

5.4.2 Investigation of significant differences between respondents reporting the various problems and benefits and those not reporting such effects included consideration of the following variables (137 variables in total).

- Age, Initiation—age at first use of all drugs (tea/coffee, tobacco, alcohol, cannabis, amphet, cocaine, crack, heroin, LSD, mushrooms, ketamine, opium, ecstasy, barbiturates, tranquillisers and solvents), Duration of using all drugs (current age minus initiation age)
- Frequency of use of all drugs, and aggregate frequencies for different drug types (coded from 0—non user to four—daily use for each drug)
- Monthly spending on all drugs, quantity normally purchased at one time
- Ratings of all drugs, plus "soap bar" resin and "skunk" (on a 0–10 scale)
- Use of cannabis (monthly use, spending, purchase, reefers/pipes per day, plus types of cannabis used, methods of using cannabis (as per cent of individual use) and number of plants grown)
- Quantitative caffeine, tobacco and alcohol consumption

5.4.3 In the tables below, only differences which were statistically significant, or approaching statistical significance ( $p < 0.1$ ), are listed. No statistically significant relationships were found where these are not specifically stated. Interpretation of results with marginal significance should be undertaken with caution, as on average seven ostensibly "significant" (@5 per cent) relationships would be expected to arise for each tranche of 137 variables. In questions on initiation ages, monthly spending, purchase and duration of use of specific drugs, plus types of cannabis and methods of cannabis use, missing values are excluded from the analysis, ie comparisons are only valid between those reporting some use of/spending on that particular drug/variety/method. Frequency/probability of use data refers to all respondents (missing values coded as "zero" ie non-user if space left blank).

Table 3

#### REPORTED HEALTH PROBLEMS ATTRIBUTED TO CANNABIS USE IDMU 1994–98 DRUG USER SURVEYS—COMBINED DATA, $n = 2794$

| Problems        | No of reports | %    | Comments/Significant differences from other respondents<br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ****— $p < .001$   |
|-----------------|---------------|------|---|
| All problems    | 588           | 21.0 | Older initiation to mushrooms†, LSD†, barbiturates*, tranquillisers* and solvents†<br>Higher frequency/probability of using caffeine***, tobacco***, alcohol***, cannabis***, amphetamine*, cocaine, mushrooms**, heroin*, LSD†, ecstasy***, tranquillisers***, all aggregate frequencies***<br>Lower spending on solvents†<br>Higher rating of caffeine*, lower ratings of tobacco**, cannabis*, barbiturates* and soap-bar resin***<br>Lower use of Lebanese resin† and African bush*, neat reefers**, pipes*, cigarettes per day†, daily tea/coffee†, higher use of tobacco reefers† |
| Memory problems | 170           | 6.1  | Higher frequency/probability of using caffeine†, tobacco***, cannabis ***, amphet*, mushrooms*, heroin*, LSD†, ecstasy**, tranquillisers*, aggregate frequency all drugs***, legal drugs**, stimulants***, hallucinogens***, depressants†, illegal drugs exc cannabis<br>Longer duration of using heroin†<br>Lower ratings of barbiturates* and soap-bar resin*<br>Lower use of African bush†, cigarettes per day*  |



| <i>Problems</i>   | <i>No of reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$  |
|---|----------------------|----------|--|
| Paranoia  | 156                  | 5.6      | Older initiation to caffeine†, base amphet*, barbiturates*<br>Higher frequency/probability of using caffeine*, cocaine*, crack†, ecstasy***, aggregate frequency all drugs**, legal drugs*, stimulants***, hallucinogens†, depressants*, illegal drugs exc cannabis*<br>Longer duration of using barbiturates† and tranquillisers†<br>Higher rating of caffeine*, lower ratings of tobacco**, alcohol†, amphet†, mushrooms†, LSD† and soap-bar resin*<br>More mushrooms gathered*, lower use of Lebanese resin† and pipes*, higher use of home-grown***, higher likelihood of injecting drug use** |
| Amotivation<br>Included those reporting apathy, laziness and related effects  | 133                  | 4.8      | Older initiation to use of caffeine*, tobacco†, mushrooms†, crack**, solvents*<br>Higher frequency/probability of using caffeine**, tobacco*, alcohol**, cannabis**, ecstasy**, tranquillisers***, aggregate frequency all drugs***, legal drugs***, stimulants*, hallucinogens**, depressants***, illegal drugs exc cannabis**<br>Higher spending on barbiturates***<br>Lower ratings of tobacco*, cannabis†, higher rating of tranquillisers†<br>Higher use of tobacco reefers†, pipes†, fewer cigarettes† and cups of tea/coffee* per day   |
| Respiratory problems<br>Included those reporting chest problems, asthma, cough, sore throat or other respiratory tract symptoms     | 116                  | 4.2      | Younger initiation to alcohol***, longer duration of using alcohol* and amphetamine†<br>Higher frequency/probability of using cannabis*, cocaine*, mushrooms†, tranquillisers†, aggregate frequency all drugs**, hallucinogens†, depressants†, illegal drugs exc cannabis*<br>Lower ratings of tobacco ** and amphet, higher rating of heroin†<br>Lower use of Asian resin† and neat reefers†, higher probability of injecting drug use†   |
| Anxiety/panic   | 50                   | 1.8      | Older initiation to tranquillisers*<br>Higher frequency/probability of using caffeine†<br>Longer duration of cannabis use*, amphet†, mushrooms†, LSD† and barbiturates*<br>Higher spending on amphetamine†, ecstasy†, barbiturates*** and tranquillisers**<br>Lower rating of cannabis†, soap-bar resin**, higher barbiturate rating†  |
| Cognitive problems<br>Included those reporting confusion, difficulty in thinking, "head f***ed" etc                                 | 49                   | 1.7      | Younger initiation to alcohol use†, longer duration of caffeine use*<br>Higher frequency/probability of using tobacco†, cannabis*, legal drugs†<br>Higher spending on mushrooms***, barbiturates*** and tranquillisers*<br>Higher rating of caffeine*, fewer reefers per day†<br>Older initiation to tea/coffee* and alcohol*, shorter duration of using tobacco†, alcohol*, cannabis† and amphet*   |
| Overdose/nausea   | 35                   | 1.3      | Older initiation to tea/coffee* and alcohol*, shorter duration of using tobacco†, alcohol*, cannabis† and amphet*<br>Lower rating of cannabis*<br>Higher use of cannabis in food*, fewer reefers*, cigarettes* and cups of tea/coffee† per day   |
| Tobacco-related problems<br>Included respiratory problems and/or nicotine addiction attributed to smoking cannabis/tobacco mixtures | 29                   | 0.9      | Earlier initiation to alcohol* and tranquillisers**, later initiation to ecstasy†<br>Higher frequency/probability of using cannabis† and mushrooms*<br>Higher rating of ketamine**, lower ratings of caffeine* and tobacco*<br>Increased use of soap-bar resin† and use in food†, lower use of African bush†   |

| <i>Problems</i>  | <i>No of reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$   |
|--|----------------------|----------|---|
| Dependence<br>Included those reporting dependence, "habit" or problems arising out of difficulties with supply | 18                   | 0.6      | Older**, earlier initiation to tobacco**, alcohol†<br>Higher frequency/probability of using cannabis†, amphet†, cocaine†, LSD*, ecstasy*, tranquillisers†, aggregate frequency all drugs*, stimulants**, hallucinogens**, illegal drugs exc cannabis**<br>Longer duration of using caffeine*, tobacco***, alcohol†, cannabis**, amphet**, cocaine†, mushrooms*, LSD**, ecstasy***, tranquillisers*<br>Higher spending on cannabis*, ecstasy*, barbiturates***, tranquillisers*** and solvents†<br>Lower ratings of tobacco† and alcohol*<br>Greater purchasing of LSD*** and amphet**<br>More reefers smoked per day† |
| Police/law problems<br>Included those attributing paranoia/anxiety symptoms to the legal situation of cannabis | 17                   | 0.6      | Higher frequency/probability of using stimulants†<br>Lower ratings of tobacco†, alcohol* and soap-bar resin*<br>More mushrooms gathered*  |
| Psychosis<br>Included manic depression and schizophrenia   | 12                   | 0.4      | Older***, later initiation to tobacco*, alcohol†, cannabis†, mushrooms***, LSD* and tranquillisers**<br>Longer duration of using tobacco**, alcohol**, cannabis**, cocaine*, mushrooms**, LSD†, ecstasy† and barbiturates†<br>Longer duration of using tobacco**, alcohol**, cannabis**, cocaine*, mushrooms**, LSD†, ecstasy† and barbiturates†  |
| Other problems   | 18                   | 0.6      | Older***, later initiation to cannabis**, cocaine*, mushrooms*, ecstasy*** and tranquillisers*<br>Higher frequency/probability of using tobacco*, cocaine*, heroin**, tranquillisers**, aggregate frequency all drugs**, legal drugs†, stimulants†, depressants**, illegal drugs exc cannabis*<br>Longer duration of using tobacco**, alcohol**, cannabis* and LSD*<br>Lower rating of soap-bar resin†<br>More pipes† and cigarettes† smoked per day  |

194 individuals reported two or more health problems

Aggregate problems: Significant relationship between aggregate problems and use of stimulants\*, and to a lesser extent depressants (including alcohol)†. None of the other aggregate frequencies approached statistical significance.

Table 4

REPORTED HEALTH BENEFITS ATTRIBUTED TO CANNABIS USE  
IDMU 1994-98 DRUG USER SURVEYS—COMBINED DATA,  $n = 2794$

| <i>Physical Health Benefits</i> | <i>No. of Reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$  |
|---------------------------------|-----------------------|----------|--|
| Pain relief                     | 170                   | 6.1      | Older**, later initiation to use of tobacco**, cannabis***, mushrooms**, ecstasy*, and tranquillisers**, earlier initiation to alcohol use†<br>Longer duration of using alcohol***, cocaine*** barbiturates† and tranquillisers**<br>Higher frequency/probability of using caffeine*, cannabis***, heroin† and tranquillisers*<br>Higher spending on barbiturates†, lower on alcohol†<br>Lower ratings of tobacco†, alcohol** and ecstasy*<br>Greater quantity of mushrooms gathered***, increased proportion of use of "other unknown" bush*, eaten neat*<br>Greater daily caffeine consumption**, lower weekly alcohol units** |



| <i>Physical Health Benefits</i>                        | <i>No. of Reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$  |
|--|-----------------------|----------|--|
| Respiratory benefit                                    | 67                    | 2.4      | Higher frequency/probability of using cannabis†<br>Shorter duration of using caffeine†, LSD†, solvents*<br>Lower spending on alcohol*, higher on LSD* and ecstasy*<br>Lower ratings of tobacco*, alcohol***, amphet†, cocaine* and tranquillisers†, higher rating of "skunk"***<br>Greater quantity purchased/gathered of ecstasy* and mushrooms*<br>Greater proportion of use of skunk*, lower proportion of tobacco-reefers*, more reefers smoked per day**, fewer units alcohol per week† |
| Improved sleep   | 46                    | 1.6      | Later initiation to tobacco*, cannabis† and tranquillisers<br>Higher frequency/probability of using alcohol†, cannabis* and depressants†<br>Longer duration of caffeine use*<br>Increased proportion of "other/unknown" bush*<br>Fewer reefers per day†  |
| Manage Addiction                                       | 19                    | 0.7      | Higher frequency/probability of using ecstasy†, tranquillisers**, aggregate frequency all drugs†, hallucinogens*, depressants†, illegal drugs exc cannabis*<br>Lower alcohol rating*<br>More reefers smoked per day*, more cups tea/coffee per day*  |
| Appetite/nausea  | 16                    | 0.6      | Later initiation to tobacco†, tranquillisers†<br>Lower frequency/probability of using alcohol†, mushrooms*, LSD*, ecstasy* and aggregate hallucinogens*<br>Lower ratings of alcohol† and ecstasy†<br>Increased quantity of cannabis purchased†, and spending on cannabis**, increased use of pipes*  |
| Epilepsy/anticonvulsant                                | 8                     | 0.3      | Lower frequency/probability of using alcohol†, amphet†, LSD*, stimulants†, hallucinogens†, depressants† and illegal drugs exc cannabis*<br>Longer duration of using alcohol†<br>Lower ratings of cocaine*, opium*, ketamine* and ecstasy*<br>Higher proportion of cannabis use as "soap bar" resin†  |
| Multiple Sclerosis                                     | 6                     | 0.2      | Older**,<br>Later initiation to tobacco* and cannabis***<br>Longer duration of using tobacco*, alcohol* and LSD†   |
| Glaucoma/vision  | 3                     | 0.1      | Older†<br>Later initiation to using mushrooms*** and LSD***<br>Longer duration of alcohol use†<br>Higher tobacco rating†   |
| Other physical benefits                                | 25                    | 0.9      | Higher frequency/probability of using mushrooms†<br>Longer duration of using amphet†, and barbiturates† shorter duration of caffeine†<br>Lower ratings of tobacco*, alcohol**, soap-bar resin***, higher ratings of mushrooms*<br>Lower proportion of use of "other/unknown" resin*, higher use of pipes*<br>Lower daily use of cigarettes*, weekly alcohol units†   |
| 42 individuals reported two or more physical benefits. |                       |          |  |
| Total Physical benefits                                | 313                   | 11.2     | Later initiation to tobacco* and cannabis**<br>Higher frequency/probability of using cannabis***, tranquillisers*, lower LSD*<br>Shorter duration of using caffeine†, longer for alcohol*<br>Lower alcohol spending**, units per week***<br>Lower ratings of tobacco*, alcohol*** and ecstasy**<br>Increased use of pipes†. More caffeine by those reporting only 1 or 2 physical benefits compared to more or none**  |

| <i>Mental Health Benefits</i> | <i>No. of Reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$   |
|-------------------------------|-----------------------|----------|---|
| Relaxation/stress relief      | 725                   | 25.9     | Older***<br>Later initiation to use of tobacco*, cannabis*, amphet**, cocaine*, mushrooms**, LSD***, ecstasy* and tranquillisers**<br>Higher frequency/probability of using caffeine***, tobacco***, alcohol***, cannabis***, amphet***, cocaine***, mushrooms*, crack†, ecstasy***, tranquillisers, all aggregate frequencies***, lower frequency/incidence of barbiturate use*<br>Longer duration of using tobacco*, alcohol***, cannabis**, amphet*, mushrooms*, LSD*, ecstasy** and barbiturates*<br>Higher spending on tobacco*, lower on amphet† and heroin†  |
| Insight/personal development  | 244                   | 8.7      | Later initiation to use of caffeine†<br>Higher frequency/probability of using caffeine***, tobacco**, alcohol†, cannabis***, cocaine†, mushrooms***, LSD**, ecstasy**, aggregate frequency all drugs***, legal***, stimulants**, hallucinogens***, illegal drugs exc cannabis**<br>Lower ratings of alcohol*, amphetamine*, ketamine**, higher rating of mushrooms†<br>Greater quantity of cannabis purchased†<br>Lower proportion of cannabis use involving Lebanese resin†, Asian resin*, other/unknown resin*, Thai bush*<br>Lower use of neat reefers*, water pipes†, other pipes† and eaten neat†<br>More reefers smoked per day** |
| Antidepressant/happiness      | 138                   | 4.9      | Older*<br>Later initiation to use of amphet*, cocaine**, mushrooms***, LSD*, ecstasy*<br>Higher frequency/probability of using caffeine**, tobacco*, alcohol**, tranquillisers†, legal drugs***, stimulants†, depressants*, and illegal drugs exc. cannabis***<br>Longer duration of using tobacco**, alcohol***, cannabis**, amphet†, opium**, LSD†, barbiturates†, and tranquilisers†<br>Higher spending on opium**<br>Higher ratings of caffeine*, cannabis*, mushrooms†, LSD***, lower rating of soap-bar resin*<br>Higher proportion of cannabis use involving "skunk"†, other/unknown bush**<br>Fewer cups tea/coffee per day*    |
| Cognitive benefit             | 81                    | 2.9      | Later initiation to use of caffeine*, earlier alcohol†<br>Lower frequency/probability of using tobacco**<br>Longer duration of use of amphet†, opium*, ketamine†, heroin*, ecstasy*<br>Lower ratings of tobacco**, alcohol*, cocaine†<br>Lower proportion of "other/unknown" resin†, higher proportion of "skunk"* and other/unknown bush†  |
| Creativity                    | 65                    | 2.3      | Later initiation to use of caffeine*, tobacco*, ecstasy†<br>Higher frequency/probability of using caffeine*, cannabis**, mushrooms*, aggregate frequency all drugs*, legal drugs*<br>Lower spending on alcohol*, higher on amphet*<br>Lower rating of alcohol†<br>Greater quantity purchased of amphet* and cocaine†<br>Lower proportion of other/unknown resin†<br>Higher proportion of use in pipes***<br>Fewer units alcohol per week*   |
| Sociability                   | 57                    | 2.0      | Later initiation to use of amphetamine*<br>Higher frequency/probability of using caffeine*, alcohol*, cannabis†, amphet*, cocaine*, LSD*, ecstasy***, aggregate frequency all drugs***, legal drugs**, stimulants***, hallucinogens**, depressants†, illegal drugs exc. cannabis**<br>Higher ratings of caffeine**, cannabis*** and mushrooms*<br>Greater quantity purchased of amphet* and cocaine†<br>Higher cannabis spending**<br>Lower proportion of use of soap-bar resin†  |



| <i>Mental Health Benefits</i> |               | <i>No. of Reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— $p < .01$ , *— $p < .05$ , **— $p < .01$ , ***— $p < .001$  |
|-------------------------------|---------------|-----------------------|----------|--|
| Sensory/perception            |               | 46                    | 1.6      | Later initiation to use of caffeine**, amphet† and solvents†<br>Higher frequency/probability of using caffeine*, mushrooms**, LSD* and aggregate hallucinogens†<br>Higher ratings of mushrooms*<br>Greater quantity of cannabis purchased***<br>Lower proportion of other/unknown resin†<br>Higher proportion of cannabis use in tobacco reefers†, and eaten with food**<br>Fewer reefers per day†   |
| Reduce aggression             |               | 39                    | 1.4      | Lower initiation to use of alcohol*, earlier use of barbiturates**<br>Lower frequency/probability of using alcohol*, higher incidence/use of solvents†, aggregate hallucinogens†, illegal drugs exc. cannabis†<br>Shorter duration of use of solvents†<br>Lower rating of opium*<br>Lower proportion of cannabis as African bush†<br>More reefers*** and pipes*** smoked per day   |
| Spirituality                  |               | 24                    | 0.9      | Older**<br>Later initiation to use of opium*, LSD†, ecstasy***<br>Higher frequency/probability of using cannabis*, cocaine*, mushrooms*, LSD*, ecstasy*, tranquillisers†, aggregate frequency all drugs†, stimulants**, hallucinogens**, illegal drugs exc. cannabis**<br>Longer duration of use of tobacco**, alcohol**, cannabis**, amphet**, mushrooms* and LSD*<br>Lower ratings of tobacco* and alcohol*, higher rating of mushrooms**<br>More reefers† smoked per day  |
| Sexuality                     |               | 16                    | 0.6      | Older***<br>Later initiation to use of tobacco*, cannabis*, amphet*, cocaine*, mushrooms**, crack*, LSD** and ecstasy***<br>Higher frequency/probability of using mushrooms* and crack†<br>Longer duration of use of tobacco**, alcohol***, cannabis***, amphet**, cocaine**, mushrooms**, heroin**, LSD*, ecstasy†, barbiturates†* and tranquillisers**<br>Higher proportion of use of Asian resin†, other/unknown bush**, water pipes*, other pipes**, eaten with food***  |
| Other                         | Psychological | 38                    | 1.4      | Later initiation to use of tranquillisers† and solvents***<br>Higher frequency/probability of using tobacco*, cannabis*, amphet*, mushrooms**, LSD**, solvents*, aggregate frequency all drugs*, legal drugs†, stimulants†, hallucinogens* and illegal drugs exc. cannabis*<br>Longer duration of use of heroin* and barbiturates*<br>Higher rating of caffeine*, lower rating of soap-bar resin†, Lower proportion of use involving soap-bar resin†, higher proportion of "other/unknown" bush†<br>More reefers smoked per day**  |
| Total                         | Psychological | 1033                  | 37.0     | Older***<br>Later initiation to use of caffeine*, amphet**, cocaine**, mushrooms***, crack†, LSD*, ecstasy***, tranquillisers*<br>Higher frequency/probability of using caffeine***, cannabis***, cocaine***, mushrooms***, aggregate frequency all drugs***, legal drugs***, hallucinogens***, illegal drugs exc. cannabis***<br>Higher frequencies among those reporting only one or two psychological benefits compared to more or none for tobacco***, alcohol***, amphet***, ecstasy***, tranquillisers**, stimulants***, depressants***<br>Longer duration of use of tobacco**, alcohol***, cannabis**, amphet*, mushrooms*, LSD†, ecstasy*<br>Lower rating of tobacco†, higher rating of cannabis†<br>Higher cannabis purchase quantity**, fewer units of alcohol per week† |

| <i>Mental<br/>Health<br/>Benefits</i>                       | <i>No. of<br/>Reports</i> | <i>%</i> | <i>Comments/Significant differences from other respondents</i><br>†— <i>p</i> < .01, *— <i>p</i> < .05, **— <i>p</i> < .01, ***— <i>p</i> < .001  |
|---|---------------------------|----------|---|
| 333 individuals reported two or more psychological benefits |                           |          |   |
| All Health Benefits   | 1,616                     | 57.8     | Older***, later initiation to tobacco**, cannabis**, amphet***, cocaine***, mushrooms***, LSD***, ecstasy***<br>tranquillisers† and solvents*<br>Higher frequency/probability of using caffeine***, tobacco***, alcohol**, cannabis***, amphet***, cocaine***, mushrooms***, heroin*, LSD***, ecstasy***, tranquillisers***, all aggregate use frequencies*** (all drugs, legal drugs, stimulants, hallucinogens, depressants, illegal exc. cannabis)<br>Longer duration of using tobacco***, alcohol***, cannabis***, amphet***, cocaine**, mushrooms**, heroin**, LSD*** and ecstasy†<br>Lower monthly spending on alcohol***, mushrooms*, heroin†, solvents†, higher spending on cannabis†<br>Lower ratings of tobacco***, alcohol***, amphet*, barbiturates*, tranquillisers† and soap-bar resin*, higher ratings of cannabis*** and mushrooms***<br>Greater amount purchased/gathered of ecstasy* and mushrooms*<br>Lower use of Lebanese resin*, other/unknown resin**, African bush†, Thai bush†, with food†, and weekly alcohol intake***<br>Increased reefers per day***, number of plants grown* and tea/coffee daily** |
| Medicinal use as main reason for cannabis use               | 78                        | 2.8      | Older (by average 5 years)***<br>Later initiation to using cannabis**, mushrooms**, ketamine†, ecstasy***<br>Lower frequency/probability of using alcohol**, ecstasy*, higher cannabis† and tranquilliser** frequency<br>Longer duration of using tobacco***, alcohol***, cannabis***, amphet**, cocaine***, mushrooms*, heroin*, LSD***, ecstasy†, and barbiturates*<br>Lower spending on barbiturates*, higher solvents***<br>Lower ratings of tobacco†, alcohol***, ecstasy* and solvents*<br>Greater number of mushrooms gathered***<br>Higher use of “other/unknown” herbal cannabis**<br>Higher use by eating “neat”***<br>Higher daily tea/coffee, lower weekly alcohol intake   |

5.5 Reasons for using cannabis

5.5.1 Although 1,616 individuals reported medicinal benefits, only 78 reported medicinal reasons (other than relaxation) as a primary motivation for using cannabis. No significant associations found.

Table 5  
REASONS FOR USING CANNABIS

| <i>Reason</i>       | <i>n</i> | <i>%</i> |
|---------------------|----------|----------|
| Relaxation          | 637      | 22.8     |
| Pleasure/recreation | 628      | 22.5     |
| Social              | 225      | 8.1      |
| Mental benefit      | 184      | 6.6      |
| Comparative risk    | 137      | 4.9      |
| Coping/escape       | 83       | 2.9      |
| Spiritual           | 82       | 2.9      |
| Medicinal           | 78       | 2.8      |
| Political           | 66       | 2.4      |
| Habit               | 26       | 0.9      |



## SECTION 6. MEDICINAL USES OF CANNABIS—LITERATURE REVIEWS

6.1 *General Observations*

6.1.1 Research on therapeutic applications of cannabis has been effectively discouraged by the legal situation during the latter half of this century. Most medical research has concentrated on potential harmful effects, and much of the best research into therapeutic uses was conducted during the 1970s. Following discovery in recent years of a “cannabis receptor”, there has been increased interest in the therapeutic potential of cannabis and its analogues.

6.1.2 Much of the debate about therapeutic use of cannabis has centred on the reduction of the raw matter to its specific chemical compounds. Studies then try to determine the exact physiological and psychological effects of each constituent on its own. This is, of course, quite in keeping with accepted modern pharmaceutical and medical practice, inclusion of cannabis derivatives in the pharmacopoeia, on the grounds that existing drugs are available with more precise or efficacious properties.

6.1.3 Such conclusions conflict with modern anecdotal reports citing cannabis in natural form as the most effective treatment in a variety of cases, as well as with long traditions of medical uses. It may be that each of the conditions treated is affected by a number of different compounds present in cannabis, both as agonists and antagonists. Many current pharmaceutical treatments rely on a cocktail of drugs to treat a single condition.

6.1.4 For example, the cannabimimetic effects of  $\Delta^9$ THC are well documented and frequently cited as arguments against the use of cannabis in therapy. Yet as long ago as 1981 reports appeared citing the presence in raw cannabis of a water soluble inhibitor of the action of THC<sup>44</sup>. Similarly, CBD has been shown to reduce the anxiety caused by high-dosage  $\Delta^1$ THC<sup>45</sup>. It has been suggested that the use of such natural inhibitors in conjunction with the active derivatives might allow the unwanted cannabimimetic effects to be negated while preserving the desired therapeutic properties<sup>46</sup>.

6.1.5 The case against cannabis on the grounds of non-specific action is only valid within the context of a broader argument against alternative therapy in general. The modern NHS and those in private medicine are already moving towards acceptance and even support of alternative and complementary medicine. Many of the treatments in this sphere include the use of similar non-specific natural remedies.

6.1.6 In 1988, US Supreme Court Judge Francis L Young in a ruling<sup>47</sup> on a petition for the rescheduling of marijuana to allow medicinal use, held that such rescheduling should occur, finding that cannabis was “one of the safest therapeutically active substances known to man”. He approved cannabis for the treatment of glaucoma, multiple sclerosis and treatment of the side effects associated with cancer chemotherapy.

6.1.7 In a 1992 report<sup>48</sup>, the World Health Organisation Expert Committee on Drug Dependence recommended that THC and related compounds be rescheduled from schedule 1 to schedule 2 of the Convention on Psychotropic Substances 1971. This effectively recognised the therapeutic value of cannabis compounds, would permit wider use in the treatment of organic diseases, and may lead to a dramatic increase in research devoted to therapeutic applications. Discovery of the “cannabis receptor” in the central nervous system and other areas<sup>49</sup> has led to an increase in recent research into the therapeutic applications of cannabinoids.

6.2 *Medicinal uses*

6.2.1 The medicinal uses of cannabis would fall into a number of categories:

6.2.2 Analgesic—this effect is now well-established and the BMA have recommended that some cannabinoids be available for prescription. (Literature review below.)

6.2.3 Anti-emetic—this use of cannabinoids (eg Nabilone) in treating the side-effects of cancer chemotherapy is well established, there is increasing evidence as to efficacy as an appetite stimulant in AIDS patients.

6.2.4 Anticonvulsant—first reported by O’Shaughnessy in 1838, there is substantial evidence for the efficacy of some cannabinoids (eg CBD) in treatment of epileptic disorders. As CBD has few psychotropic effects, there would appear to be no logical reason for preventing or discouraging research and/or clinical trials of this cannabinoid. (Literature review below.)

6.2.5 Anxiolytic—relief of stress and relaxation is the most commonly-reported “therapeutic” benefit by most users. However, stress levels can increase dramatically in naïve users exposed to the drug. (Literature review below.)

6.2.6 Bronchodilator—the BMA report covers potential use of cannabinoids in the treatment of asthmatic disorders. (Literature review below.)

6.2.7 Opiate/Alcohol dependence—there is a limited evidence suggesting that high doses of cannabis may ameliorate the opiate withdrawal syndrome, and the anticonvulsant action of cannabinoids may assist during detoxification of individuals following withdrawal of opiates or alcohol. While there is anecdotal evidence of individuals successfully using cannabis as a long-term substitute for opiates or alcohol, the scientific evidence does not lead to great optimism for this aspect of potential treatment. (Literature reviews below.)

### 6.3 *Historical and Cultural Uses*

6.3.1 Culpepper (1616–1654)<sup>50</sup> advocated the use of a decoction (tea) of the cannabis hemp root in the treatment of “the pains of the gout, the hard humours of knots in the joints, the pains and shrinkages of the sinews, and the pains of the hip”. In other words, for what we would now class as arthritis.

6.3.2 Rubin<sup>51</sup> reviewed evidence of traditional medicinal usage of the plant from a variety of native cultures. The Pan Ts’oo Ching, a Chinese pharmacopoeia dating from the second century AD, stated that an infusion of cannabis “undoes rheumatism”. Rabelais the classical French author, physician and botanist suggested that the “root, boiled in water, softens hardened sinews, contracted joints . . . (and) gouty swellings”.

6.3.3 O’Shaughnessy<sup>52</sup>, in the first modern (1837) treatise on the medical use of cannabis, described the widespread medicinal use of the drug in India, including cases where he had successfully used the drug for the relief of convulsions.

6.3.4 Mattison<sup>53</sup> reported of cannabis that “its analgesic virtue is shown in allaying the intense itching of eczema, so as to permit sleep.” He cites clinical study of 1,000 patients treated with cannabis as a hypnotic (sleep inducing agent) found complete success in 53 per cent and partial success in 22 per cent of cases. Reynolds<sup>54</sup>, personal physician to Queen Victoria, recommended cannabis for use in “senile insomnia”.

6.3.5 Mikuriya<sup>55</sup> reviewing 19th Century and early 20th Century medical reports, quotes 1968 correspondence from Parke Davis<sup>56</sup>, who produced medicinal cannabis products until the 1930s, suggesting that an effective dose of an alcoholic tincture was 1ml per kilo body weight, and of the solid extract (ie the purified cannabinoids) 4mg per kilo was required as an oral dose.

### 6.4 *Cannabis and pain relief*

6.4.1 A review of the use of cannabis as an analgesic (pain relief) agent was undertaken by Professor Rafael Mechoulam<sup>57</sup>. A number of researchers using  $\Delta^9$ THC injections in mice, with dosages of 5-80 mg/kg, have observed significant antinociceptive (pain relieving) activity against thermal, mechanical, electrical and chemical stimuli. In some cases the effect of cannabinoids was stronger than with opioid preparations, and other researchers noted a flat response curve (ie once the effective dose level is reached, further dose increases cause no additional effect). Other researchers have found cannabis to potentiate the analgesic effects of opiates<sup>58</sup>. Significant analgesia has been produced in animals with injections into the brain stem and spinal cord.<sup>59 60</sup>

6.4.2 The dosages required to produce detectable pain relief in animal models were substantially in excess of dosages encountered in normal social use (typically 0.1-1.0 mg/kg). The effective dose of THC in the early mouse studies (approx 5mg/kg) would be the equivalent of an average 70kg man consuming 350mg THC, or smoking 10 grams of cannabis with a potency of 3.5 per cent.

6.4.3 Mechoulam found inconclusive results on pain relief from human subjects, although the dosages in most studies were lower than those found effective in animal models. He concluded that there was “significant analgesic activity” from THC, remarking that the lack of any physical dependence was “a plus”, although he was concerned about the “psychotomimetic” effects (ie the high) particularly for individuals unused to the drug. In an earlier review<sup>61</sup> Mechoulam had considered the traditional use of cannabis preparations as analgesic and anti-rheumatic agents to have “some modern substantiation”.

6.4.4 Noyes et al<sup>62</sup> found a clear dose-related analgesic effect from oral administration of THC. In a second study<sup>63</sup> the analgesic effect was found to be six times as powerful as that of codeine, with 20mg THC producing significant pain relief for over five hours. He considered the side effects (sedation and light-headedness) to mitigate against wider clinical use. However, his subjects were inexperienced with marijuana use and as such may have found the psychological effects of the high more disturbing, and thus less tolerable, than experienced users. Milstein et al<sup>64</sup> found that experienced marijuana users exposed to approximately 7.5mg THC by inhalation, achieved a greater analgesic effect than naive subjects and were less likely to report adverse side effects. Whether this increased response is due to more efficient inhalation techniques in the experienced group, or through a “reverse tolerance” whereby THC has a greater effect in habitués, is not clear.

6.4.5 In Judge Young’s report<sup>65</sup> numerous case histories were described outlining the use of cannabis to reduce muscle tension (spasticity) in individuals with multiple sclerosis or spinal injury. The potential efficacy of cannabis in treatment of MS is increasingly accepted by patients and medical practitioners alike. Ungerleider et al demonstrated clear dose-related reduction of spasticity with doses of 7.5 to 15mg THC<sup>66</sup>.

6.4.6 Pertwee<sup>67</sup> reports a number of patients suffering spinal injury or multiple sclerosis claiming cannabis relieves spasticity and pain associated with muscle spasms more effectively than conventional muscle relaxants and with more tolerable side effects. Several clinical trials have supported these claims<sup>68 69 70</sup>, indicating that oral THC or inhalation of cannabis smoke can relieve muscle pain and spasticity.

6.4.7 Cannabis was the treatment of choice for migraine in the last century, and a modern report<sup>71</sup> has supported the efficacy of the drug in this respect.



6.4.8 The BMA report made the following recommendations concerning cannabinoids and pain:

“The prescription of Nabilone, THC and other cannabinoids should be permitted for patients with intractable pain. Further research is needed into the potential of cannabidiol”

6.4.9 Our own recent study of cannabis users<sup>72</sup> asked respondents to report any physical or mental health problems and/or benefits which they attributed to cannabis use. Thirty two individuals cited “pain relief” as the main benefit they received, the fourth most common benefit reported (after relaxation (n = 89), stress relief (n = 67) and improvements in personal development and outlook (n = 36)). Two individuals specifically mentioned use of cannabis as a muscle relaxant.

## 6.5 *Antiepileptic/Anticonvulsant effects*

6.5.1 The anticonvulsant properties of cannabis were first described in 1837 by O'Shaughnessy<sup>73</sup>, who described its successful use in treating spasms caused by tetanus and infantile convulsions. In 1960 an enquiry by the Ohio State Medical committee<sup>74</sup> took evidence from Professor Miller of Edinburgh as to its effectiveness in treating “inordinate muscular spasm” causes by tetanus, and from a Dr Kincaid on the successful treatment of fits in three persons suffering epilepsy, two of long term organic and one of traumatic origin, two other patients showed no improvement. In 1890 Reynolds<sup>75</sup>, personal physician to Queen Victoria, who described its effectiveness in treating clonic and choreoid spasms of the epileptiform type, described it, for some patients, as “the most useful agent with which I am acquainted” for treating “attacks or violent convulsions . . . (which) may recur two or three times in the hour . . . may be stopped at once by a full dose of hemp”. However, he did not consider it appropriate for all patients, particularly those with severe epilepsy as a result of “organic lesion or eccentric irritation”.

6.5.2 In 1949, Davis & Ramsey<sup>76</sup> tested two homologues of THC in a clinical trial on five institutionalised epileptic children, three responded as well as to previous therapy, with two virtually symptom free. The authors considered that the cannabinoids deserved further trial in non-institutionalised epileptics.

6.5.3 In a 1950 paper, Loewe<sup>77</sup> considered a number of cannabinoids to show antiepileptic activity, and considered that these showed much greater potency (up to 150 times) and an incomparably greater margin of safety than diphenylhydantoin.

6.5.4 Consroe et al<sup>78</sup> reviewed numerous animal experiments showing anticonvulsant or antiepileptic activity in rat, mouse, frog, cat, baboon and gerbil, some studies showing the development of tolerance to the anticonvulsive effects, and also experiments showing convulsant activity in rat, dog, monkey, cat and rabbit, several of which involved extremely high THC doses of 60-3,600mg/kg. Their own experiments confirmed anticonvulsant and convulsant activity, and recommended further research in this area. In a previous study the same author<sup>79</sup> found that a single epileptic patient receiving conventional anticonvulsant medication (phenobarbitone and diphenylhydantoin) was only able to control seizures when illicit marijuana was used (2-5g per day) in conjunction with the conventional drugs. In 1981, Consroe & Fish<sup>80</sup> considered Nabilone (a synthetic cannabinoid) to be 7.5 times as effective as THC in *provoking* convulsions in a hypersensitive rabbit model. CBD provoked no seizures.

6.5.6 In a double-blind clinical trial of CBD, Cunha et al<sup>81</sup> found it to be effective in abolishing or reducing seizures in seven out of eight subjects receiving 100mg daily, whereas only one out of seven placebo controls reported any improvement. Concluded that CBD had a beneficial effect in patients suffering from secondary generalised epilepsy, who did not benefit from known antiepileptic drugs.

6.5.7 Karler & Turkanis<sup>82</sup> considered both  $\Delta^9$ -THC and 11-hydroxy THC (metabolite) to have anticonvulsant activity, and noted that CBD prolonged the effects of common antiepileptic drugs such as phenobarbitone and diphenylhydantoin, suggesting that the effectiveness of these drugs could be increased in combination with CBD, and considered CBD to have the most promising antiepileptic potential of the cannabinoids. In a later study<sup>83</sup>, the same authors suggested the widespread and specific anticonvulsant effects of stereoisomeric cannabinoids was evidence of a specific receptor, and considered CBD to be the most non-psychoactive agent, causing a depression of seizure spread. They considered the effect of THC to be attributable to the three major metabolites, with CBD showing a clear dose (brain concentration) response curve, whereas THC showed delayed responsiveness, consistent with the increase in metabolites following THC breakdown. There were considerable species differences in response between rat, mouse and frog. They concluded that CBD met all the requirements as a potentially useful drug in the treatment of epilepsy, being devoid of psychotoxicity, showing anticonvulsant selectivity, and appeared to be free of CNS excitatory effects characteristic of most anticonvulsants.

6.5.8 In a large-scale epidemiological study, Ng et al<sup>84</sup> found marijuana use to be protective against the development of first onset seizures, however there was no indication of the dosages used, differentiating only between “ever” used and used within the previous 90 days.

6.5.9 A critical review of the accepted anticonvulsant activity of cannabinoids by Feeney et al<sup>85</sup>, considered previous studies to be inconclusive, with most showing some reduction in seizure activity, although in some individual subjects the frequency or duration of seizures could be exacerbated. Further experiments on dogs, using daily doses of 0.5 to 5.0mg/kg THC, claimed to show a dose-related increase in duration of EEG seizure activity, with 20mg/kg showing the greatest increase (equivalent to 1.4g pure THC



for a 70kg human, or 14g-28g of cannabis at 10 per cent and five per cent purity respectively). They considered their data to show an increased risk of seizures in persons with pre-existing pathology. However these studies involved small numbers of animals, and CBD dosages failed to increase seizure activity significantly over controls, and the authors considered Cannabidiol (CBD) to be worthy of further study.

6.5.10 In a 1976 survey of epileptic patients, Feeney<sup>86</sup> found a number of marijuana users, most reporting no effect, one that symptoms decreased, one that marijuana “caused” his seizures. In a later report, Feeney<sup>87</sup> considered THC to have both convulsant and anticonvulsant action, provoking symptoms including grand mal seizures in epileptic beagles, but blocking electroshock seizures in rats at comparable doses. Considered CBD to exert anticonvulsant effects with no convulsant or psychotropic action, and recommended clinical trials with no convulsant or psychotropic action, and recommended clinical trials of CBD to test anticonvulsant action in epileptic humans.

6.5.11 Keeler & Riefler<sup>88</sup> reported a single case history of seizure-free epileptic finding symptoms recurring following a period of marijuana use, called attention to the risk of using marijuana for seizure-prone individuals. Perez Reyes et al<sup>89</sup> found an increase of EEG spikes following iv administration of 40mg cannabinal to a single 24 year old epileptic patient. Earlier case studies<sup>90</sup> included one epileptic whose seizures were considered to have been precipitated by an experimental exposure to cannabis extract.

6.5.12 Grinspoon<sup>91</sup>, after reviewing other studies reported above, noted two cases histories of individuals who had successfully used marijuana for treating epileptic symptoms, the first found marijuana abolished frequent petit-mal seizures which had been unresponsive to other medication, the other found that cannabis abolished grand-mal seizures, and substantially reduced petit mal seizures, enabling him to reduce his conventional medication by over 50 per cent. The seizures returned during the patient’s imprisonment on a marijuana cultivation charge.

6.5.12 *Summary on anticonvulsant effects.* The studies show that cannabis may have beneficial effects for some epileptic patients, primarily attributable to CBD and metabolites of THC. In particular, CBD appears to show the most consistent anticonvulsant action, and has been shown to increase the effectiveness of prescribed anticonvulsant medication. Most studies have reported the therapeutic effectiveness to differ between individuals or between different types of epilepsy, with some individuals receiving no benefit or adverse effects, while others can show a complete cessation of symptoms. If an individual has experienced a positive effect on the frequency and/or severity of symptoms following cannabis use, it is probable that the drug would have contributed to this effect. However, I would consider cannabis resin, with a relatively high CBD content, possibly to provide a greater benefit than indoor herbal cannabis, which typically has relatively low CBD.

## 6.6 Cannabis and Stress Relief/Relaxation

6.6.1 In our recent surveys, relaxation and stress relief were overwhelmingly the most commonly preceived benefits of cannabis use. However, the Department of Health identifies panic attacks and anxiety as effects of acute cannabis intoxication, particularly among naive users, as justification for previous refusals to permit the prescribing of cannabis.

6.6.2 Recent advances in fundamental cannabinoid research have been interpreted as indicating a common modality of action of cannabis and opiate drugs, in that naloxone (an opiate antagonist) blocks cannabinoid-induced dopamine release in the limbic system (a primitive brain structure associated with control of emotion and mood)<sup>92</sup>. A cannabinoid antagonist administered to rats, pre-treated with a powerful synthetic cannabinoid agonist, can precipitate corticotrophin releasing factor (CRF), which is held to be the mechanism responsible for mediating the psychological aspects of drug withdrawal symptoms, and leading to anxiety-type behaviours<sup>93</sup>. This was interpreted as demonstrating a cannabis withdrawal syndrome. However the potency of the synthetic cannabinoid used was many times that of THC, and the administration of an antagonist (blocker) would not effectively mimic the gradual decrease in plasma THC which occurs with cessation of normal use. The fact that a potent cannabis blocker caused anxiety symptoms in rats would be consistent with a general diminution of anxiety levels arising from cannabis use.

6.6.3 Laurie<sup>94</sup> reported that in a few cases “anxiety, which may approach panic, often associated with a fear of death or an oppressive foreboding, is infrequently seen, usually giving way to an increasing sense of calmness . . . to euphoria”. Grinspoon refers to the initial state as a “happy anxiety” where the experience is internally redefined as pleasurable. Rosenthal et al<sup>95</sup> report that panic reactions and anxiety are rare, and most commonly found with overdose (particularly from oral preparations), in naive users, or in those who do not like the effects of marijuana, and attributed the incidence of anxiety reports with Marinol (dronabinol—pure THC) to the lack of CBD within the preparation. Mikuriya<sup>96</sup> considered that “the power of cannabis to fight depression is perhaps its most important property”. Patients were reported to self-medicate with cannabis rather than use benzodiazepines as the former produced less dulling of mental activity. The authors cited one study where marijuana was found to increase anxiety in naive users, but to decrease anxiety in experienced users, and another of 79 psychotics who used marijuana recreationally and reported less anxiety, depression, insomnia or physical discomfort<sup>97</sup>. They concluded that natural marijuana—containing CBD and THC—appeared more effective than THC alone in treating depression, and that patients suffering stress as a result



of pain or muscle spasms would be most likely to be helped by the drug. They differentiated the use of cannabis to cope with everyday life stresses from the use of benzodiazepines in treating “severe anxiety disorders” with an organic aetiology.

6.6.4 Bello<sup>98</sup> in a passionate treatise on the benefits of cannabis for physical and mental health, likened the anxiolytic effect of marijuana to a state of relaxed alertness brought on by “balancing” the autonomic nervous system.

6.6.5 Explanations of the panic and anxiety experienced by some naive users exposed to cannabis would include a low tolerance to the drug, and “set and setting” ie a drug taken in the course of a laboratory experiment would provide different expectations of an experience to an informal party or gathering of friends. Secondly, the increase in heart rate can be interpreted by some older naive users as a heart attack and cause panic attacks<sup>99</sup>, this “tachycardia” is normally associated with a reduction in blood pressure. Some individuals may be more susceptible to the effects of cannabis than others, and those whose initial experience is unpleasant may be more likely to discontinue use of the drug. By contrast, many first-time users fail to notice the influence of the drug.

6.6.6 Thompson & Proctor<sup>100</sup>, treating withdrawal conditions, noted the synthetic cannabinoid pyrahexyl to produce significant increases in alpha brain waves, indicating increased relaxation, and Adams reported similar results<sup>101</sup>. However Williams et al found no significant increase in alpha activity either with pyrahexyl or smoked marijuana<sup>102</sup>.

6.6.7 Davies et al<sup>103</sup>, in a study of cancer patients, considered the management of stressful patients to have been improved by oral THC. However a study of intravenous THC used as a premedication for oral-facial surgery<sup>104</sup> found that patients showed pronounced elevation of anxiety, and considered noxious stimuli to be more painful. Mechoulam<sup>105</sup> considered a number of synthetic cannabinoids to be worthy of investigation as potential sedative-relaxants.

6.6.8 Musty<sup>106</sup> compared the effects of THC, CBD (cannabidiol) and diazepam (valium) on anxiety-related behaviours in mice. THC produced similar reductions in anxiety behaviours to diazepam, however the effect of CBD was more pronounced than either in measures of shock-avoidance, grooming and reduction of delirium tremens in alcohol-withdrawn mice. Both THC and CBD produced dose-related reductions in ulcer formation in stressed mice. However in all tests the CBD dosages used were higher than THC dosages.

6.6.9 Mechoulam reviewed studies of Nabilone (synthetic cannabinoid) on anxiety, finding two studies which suggested a superior effect on anxiety, mood and concomitant depression, whereas two other studies found little or no effect. Benowitz & Jones<sup>107</sup> reported initial tachycardia and hypertension in volunteer subjects administered up to 210mg THC per day, but found development of tolerance to tachycardia and CNS effects over the 20 day experiment, with blood pressure reduced and stabilised at around 95/65. Fabre & McLendon<sup>108</sup> reported a dramatic improvement in anxiety in the nabilone-treated group compared to placebo. Nakano et al<sup>109</sup> reported anti-anxiety effects of nabilone and diazepam in a controlled trial of experimentally-induced stress, but was unable to conclude which was more effective due to differences in dosage and metabolism. Hollister<sup>110</sup> reported these and other nabilone studies<sup>111</sup> indicating significant anti-anxiety effects of low doses, and commented on the scarcity of studies of potential anti-anxiety effects of cannabinoids.

## 6.7 Depression

6.7.1 Depression is a term used to describe a variety of different disorders characterised by lowering of mood, disinterest in ones surroundings or condition, fatigue, and loss of appetite and/or personal neglect. Only when depression is serious is it normally considered a psychiatric disorder requiring treatment. Most drug treatments for clinical depression involve use of tricyclic antidepressants (eg amitriptyline), monoamine oxidase inhibitors (eg isocarboxazid) or more recently fluoxetine (Prozac), both of which boost levels of brain catecholamines (stimulant neurotransmitters including noradrenalin or serotonin).

6.7.2 Cannabis products have long been considered to be effective in the treatment of depressive disorders, in 1845 it was recommended for melancholia (with obsessive rumination) and mental disorder in general<sup>112</sup>. In 1947 Stockings<sup>113</sup> found improvements in 36 out of 50 depressed mental patients treated with a synthetic cannabinoid.

6.7.3 Bolls<sup>114</sup> reported a case of post-natal depression successfully treated by a large oral dose (4g of alcoholic cannabis tincture) and counselling. The subject reported anxiety at the peak of the drugs effect, however the study involved a single case, was not controlled under current scientific methodology, and it could not now be concluded whether any recovery was due to the drug, the psychotherapy, or would have occurred in any event.

6.7.4 Kotin et al<sup>115</sup>, in a double-blind experiment, found no effect on moderate to severe depression from relatively high doses (0.3 mg/kg) of THC. Grinspoon considered cannabinoids to be of promise where depression is secondary to some life event (reactive depression) rather than a primary diagnosis, but did not consider general optimism about such treatment to be justified by the state of knowledge in 1977.

6.7.5 Regelson et al<sup>116</sup> reported a number of significant effects in a controlled study of THC in terminal cancer patients, including a reduction in depression, greater emotional stability, more self-reliant/less

dependent, less suspiciousness, increased forthrightness, less apprehension, more normal level of control and more tranquil/relaxed, however two patients who discontinued the study reported fear and anxiety, confused thinking and dissociation. The authors commented that such effects would appear to be confined to a susceptible population.

6.7.6 Grinspoon<sup>117</sup> considered some patients who fail to respond to traditional antidepressant drugs, or who find the side-effects of these unbearable, to have been helped by illicit marijuana use, quoting three case studies all involving long histories of severe clinical depression, all treated unsuccessfully with all types of antidepressive medication, and all now living normally through use of cannabis, twice daily in one case, on reappearance of symptoms in the others, each attributing the improvement to greater self-insight, a reduction of a negative self-image, and/or a general euphoria arising from cannabis intoxication.

6.7.7 Conclusions re Anxiety and Depression: There is a great deal of anecdotal evidence to suggest that cannabis may have a beneficial effect on mood disorders such as mild anxiety or depression. However, the results of scientific studies are inconclusive, and the anecdotal reports cannot be reliably confirmed at the present time. In particular the human studies which have been cited in support of such psychological benefits either used synthetic cannabinoid homologues, or failed to use the double-blind experimental methodologies now required to eliminate possible bias in the experimenters or subjects.

6.7.8 Whereas experienced cannabis users quote “relaxation” as the most commonly perceived health benefit derived from the drug, many novice users experience a severe bout of anxiety which can approach a panic attack. These are very rare among experienced users of the drug, and can often be attributed to a hostile environment and/or negative expectations of the drug’s effects.

6.7.9 The effect of cannabis and cannabinoids is not adequately predictable for dosage regimes to be developed for the general population. Cannabis affects different people in different ways—one person may feel relaxed when the next might feel anxious and paranoid—and could not be used in the treatment of mental disorders without close monitoring of the effects on individual patients. However, where conventional medications have failed to control the symptoms adequately, there may be a case for trial use of cannabis to determine whether the drug could aid existing treatment or replace drugs with unwanted side effects.

6.7.10 The most recent research into cannabinoid neurochemistry provide qualified support for the view that cannabis drugs can promote relaxation and a less stressful mental state. However whether this is a learned effect, or an effect of tolerance to the drug’s effects and the avoidance of withdrawal (mediated by CRF release in the amygdala), cannot yet be determined.

6.7.11 I would not consider the case yet to be made for the widespread prescription of cannabis as an antidepressant or antianxiety medication. There is clearly a need for much additional research into the efficacy of cannabis on these conditions. Where many cannabis users report a general improvement in mood, others find the experience highly disturbing, and the risks of prescribing the drug to unsuitable individuals may well outweigh the potential benefits.

## 6.8 *Therapeutic research in the treatment of Asthma*

6.8.1 Cannabis and cannabis extracts have a long history in the treatment of asthma-related complaints, as long ago as 1695<sup>118</sup>, including an enquiry by the Ohio State Medical Committee in 1860<sup>119</sup> where oral dosage of one grain of tincture every three hours produced “almost magical” relief from asthma symptoms. J. Russell Reynolds, personal physician to Queen Victoria, writing in 1890<sup>120</sup> stated that “in some cases it relieves spasmodic asthma”, and Mattison, in 1891, reported similar findings<sup>121</sup>.

6.8.2 Modern research has tended to confirm traditional therapeutic use as an anti-inflammatory and bronchodilator agent. Vachon et al<sup>122</sup>, using volunteer asthma patients, found that smoke from low-potency material (1.9 per cent and 0.9 per cent THC) showed highly significant bronchodilator effects, which did not appear to be dose related, lasting for up to 90 minutes after administration.

6.8.3 Tashkin et al<sup>123</sup> in double-blind experiments using smoked cannabis with 2 per cent or 0 per cent THC (0 per cent—placebo—all cannabinoids extracted before administration), as well as 15 mg synthetic THC administered orally, found increases in specific airway conductance (bronchodilation) with smoked and oral drug conditions, and concluded that the 0 per cent THC placebo may contain some as yet unidentified bronchodilator, as there was no broncho-constriction, which might have been expected in asthmatics following inhalation of particulate matter. They concluded that THC was effective in relieving exercise-induced bronchospasm, with the duration of the bronchodilatory action lasting from two hours to four hours after administration. Oral THC produced significant, but less pronounced, effects. In 1977<sup>124</sup> the same team used aerosolised THC in 5 mg and 20 mg doses, producing similar and significant bronchodilation after all doses, with the lower dose producing fewer physical (tachycardia) or psychological (high) side effects than the higher dose or smoked marijuana. The effect was slower in onset but longer in duration than isoproterenol, a conventional bronchodilator agent. Williams et al<sup>125</sup> also concluded that THC and salbutamol (ventolin) were equally effective in improving ventilatory function one hour after administration by aerosol, with THC having the longer duration of action.



6.8.4 Abboud and Sanders<sup>126</sup> found that bronchodilator effects were unreliable when 10mg oral THC was used, some slight increase in airway conductance was noted although one patient developed severe bronchoconstriction.

6.8.5 Reviewing the evidence in 1986, Graham<sup>127</sup> concluded that THC is an active bronchodilator with a different mode of action from the common preparations such as salbutamol and terbutaline, and active when ingested orally or by inhalation. Oral use (2mg to 20mg in a sesame oil capsule) was slower in onset than inhalation, which although not ideal, due to the particulate matter in smoke, could produce swift relief from symptoms. Higher amounts—ie 50–75mg of THC—showed a dose-related effect. Tests of CBN (600mg) and CBD (1200mg) showed these cannabinoids not to have bronchodilator activity. Prolonged administration produced no evidence of clinical tolerance to any of the actions of THC. Speculated that the action of THC may involve suppression of the release of endogenous substances causing asthma (eg SRS-A), rather than inhibiting their activity.

## 6.9 *Cannabis and Opiate withdrawal*

6.9.1 Cannabis has frequently been accused of leading its users to try harder drugs, specifically opiates. While there has never been any evidence of a causal relationship between cannabis use and heroin addiction, there is increasing evidence for some interrelationship between the effects of the two classes of drugs, and, paradoxically, for the efficacy of cannabis as an aid to opiate withdrawal. The fact remains, however, that research shows that up to two thirds of opiate users are also cannabis users<sup>128 129</sup>. The following represents a review of the available literature, plus novel analyses of data gathered from my own surveys of regular cannabis users.

6.9.2 The effect of cannabis in reducing the severity of opiate withdrawal symptoms was widely-described in the 19th century. In the very first volume of the *Lancet*, Birch<sup>130</sup> reported using 300mg cannabis extract daily to treat withdrawal symptoms in a young opium (laudanum) user, noting “improved appetite and sound sleep”, strengthened pulse and a complete physical recovery within six weeks. Mattison<sup>131</sup> recounted 10 years experience in treating opium and morphine addicts, and considered it to be “an efficient substitute for the poppy. Its power in this regard has sometimes surprised me”. One long term morphine injector, with a habit broadly equivalent to over 2g per day of “street” heroin was stated to have recovered with 10 doses of fluid extract of “Indian hemp”. The author William Burroughs wrote in 1953<sup>132</sup>

“I once kicked a junk habit with weed (Marijuana). The second day off junk I sat down and ate a full meal. Ordinarily, I can’t eat for eight days after kicking a habit.”

6.9.3 Mikuriya<sup>133</sup> reports successful use of 120mg synthetic THC (dronabinol) per day (oral in sesame oil) to withdraw a patient from a 70mg/day methadone addiction. There have been a small number of reports of self-medication of cannabis by withdrawing addicts<sup>134</sup>, and “de-escalation”, ie reducing opiate use in favour of cannabis use over the long term<sup>135</sup>. I have spoken with heroin addicts who had smoked very large quantities of cannabis during the acute withdrawal phase, reporting the symptoms to be more tolerable, thus enabling them to complete the detoxification period successfully.

6.9.4 Chesher *et al*<sup>135</sup> found that  $\Delta^9$  THC reduced the severity of a number of symptoms associated with the quasi-morphine withdrawal syndrome in rats, concluding that the effects were not due to sedation, that absence of naloxone activity indicated the effect to be independent both of the opiate receptor, and of dopaminergic neurotransmitter systems. A later study<sup>137</sup> found that cannabinol (CBN) was also effective in reducing such symptoms, but not cannabidiol (CBD). THC was also found to decrease naloxone-induced withdrawal symptoms in rats<sup>138</sup>, and other studies have found similar effects in rats<sup>139</sup>, mice<sup>140</sup>, guinea-pigs and dogs<sup>141</sup>. Radouco-Thomas<sup>142</sup>, studying hypersensitive mice, found morphine to show opposite effects between THC-pretreated and control mice, with substantial increase in locomotion following the morphine administration in THC animals, and sedation in controls.

6.9.5 Pertwee<sup>143</sup> reviewed the interactions between opiate antagonists and cannabinoids, finding some attenuation of naloxone activity, and enhancement of morphine activity in a variety of laboratory animals. Recent research suggests that the activity of cannabis is caused by binding to a specific cannabinoid receptor<sup>144</sup>, which would normally bind to an endogenous “cannabinoid” inhibiting the metabolism of cyclic adenosine monophosphate (c-AMP)<sup>145</sup>. Cyclic AMP influences the degree to which the binding of neurotransmitters on opiate (and other) receptors causes the firing of the target neurones. Put simply, it affects the sensitivity of neurones to chemical stimuli. Cohen<sup>146</sup> considered the attenuation of opiate withdrawal symptoms by clonidine to be due to opening of potassium channels mediated by c-AMP in the *locus ceruleus*—a group of cells extending from the brainstem to the midbrain, close to the cerebellar peduncles and the vagal nucleus (which controls stomach activity), and which are closely exposed to substances within cerebrospinal fluid<sup>147</sup>. Gold and Miller<sup>148</sup> note that both morphine and THC caused similar changes in dopamine activity, and postulate that the reinforcing potential of both drugs had a common neurochemical basis.

6.9.6 In 1990 Navaratnam<sup>149</sup>, in a study of adjunctive drug use of 249 heroin users, discovered that two thirds of these were using cannabis as an adjunctive drug with the primary aim of increasing the euphoric effects of the heroin, only a minority used cannabis as a way of helping with withdrawal symptoms. Unlike heroin and benzodiazepines, alcohol and cannabis were usually only taken in the company of friends. The



combined use of opiates and benzodiazepines in the last 12 months and last 30 days was higher than the combined use of opiates with alcohol or opiates with cannabis. Alcohol and cannabis, if used, were usually taken after opiate use, while benzodiazepines were used concomitantly with opiates.

6.9.7 In a recent UK study by Jackson<sup>150</sup> 40 male clients from both non-statutory and statutory agencies in North Yorkshire were asked to complete a questionnaire concerning their cannabis use. The study included both current and ex-users of opiates and covered users of heroin as well as those using methadone. The clients were specifically invited to provide information about their adjunctive use of opiates and cannabis and its uses in dealing with opiate withdrawal, the availability of cannabis to heroin users and on the motivation to start using heroin during a perceived lack of cannabis.

6.9.8 The study indicated that opiate users combined cannabis with their use of heroin or methadone for specific reasons. Most frequently quoted was as an aid to sleeping, or as a replacement for benzodiazepines. There was little support for the idea that cannabis relieved the physical symptoms of opiate withdrawal (indeed, it was commonly seen as making things worse).

6.9.9 Cannabis was regarded favourably as treatment for the psychological aspects of the process, especially as an adjunct to methadone during withdrawal of heroin. In such cases it was seen as being able to help prevent the purchase of black market heroin by fulfilling some of the addict's mental needs.

6.9.10 Similarly, a study by Saxon<sup>151</sup> found methadone patients who were consistently THC positive had a smaller percentage of urines positive for other drugs.

6.9.11 With regard to the social aspect of cannabis/heroin interaction, the Jackson study suggested, perhaps surprisingly, that heroin users felt that the cannabis using society had cut them off in many ways. The respondents are reported as "feeling quite isolated from the cannabis using scene, all seeing it as a completely separate culture, with its own set of dealers and a closed door attitude to heroin users. The general view was that cannabis users did not associate themselves with harder (heroin, cocaine) drug users and would not welcome them into their circle, certainly not to the extent where heroin could be used in these circles."

6.9.12 The third major area of the study touches, on the "gateway" theory. When asked if they knew people who had started using heroin as a result of the lack of cannabis, 63 per cent said they knew of at least one person who had started this way (59 per cent of these saying they knew some people and 33 per cent knew lots of people). This was also confirmed by 16 of the 40 clients questioned having bought heroin themselves at times because there was no cannabis around. However, this does not necessarily support the contention that cannabis use *per se* predicates toward heroin use.

6.9.13 Di Chiara's recent paper<sup>152</sup> (among others) has excited much media attention with the revelation that  $\Delta 9$ -THC and heroin both affect the same area of the brain, boosting the levels of dopamine in the nucleus accumbens.

6.9.14 The popular press, broadsheet and tabloid alike, ran stories implying that the paper had somehow proven a physiological basis for "escalation". However, as the less populist journals such as the New Scientist pointed out, Di Chiara's paper itself stated that

"... both  $\Delta 9$ -THC and heroin can be added to the list of drugs of abuse (morphine, cocaine, amphetamine and nicotine) that increase DA transmission preferentially. . .".

6.9.15 The New Scientist pointed out that the group's own previous research has also shown the same Dopamine surge with alcohol. As the editorial<sup>153</sup> explained:

"There are two problems with the idea that smoking cannabis may prime the brain for dependence on harder drugs. Number one: there is no direct evidence. Number two: if cannabis does behave this way, then by the researchers' own logic one would expect alcohol and nicotine to do the same, for all three substances push the same dopamine button in the brain by very similar chemical mechanisms."

6.9.16 This view is upheld by such reports as Nace<sup>154</sup> where studies of 101 multi-drug using soldiers showed that prior to the onset of heroin addiction, relatively few differences in drug using patterns existed between those addicted to heroin and those not, the differences emerged after the initiation of heroin.

6.9.17 The theory of social escalation (that cannabis users turn to heroin because the drug scenes cross over, and that such progression disappears when the markets are separated) does not seem validated by the Jackson study. 75 per cent of respondents claimed that it was harder to find cannabis to buy than heroin and nearly 95 per cent of those expressing a view felt that cannabis and heroin were not sold by the same dealers.

6.9.18 These figures prompted the report to conclude that a significant section of the drug using population were finding it easier to buy hard drugs than cannabis. Considering the fact that many hard drug users finance their habit through the sale of their drug of addiction, it was suggested that this could potentially lead to an increase in the incidence of hard drug abuse.

6.9.19 Certainly this contrasts starkly with figures from Holland<sup>155</sup> where the public at large view cannabis in a tolerant way and hence users of it are not subject to the problem of a criminal record or the stigma of treatment in a psychiatric hospital. This has resulted in fewer and fewer young people swapping from soft to hard drugs, the percentage of addicts younger than age 22 dropping from 14.4 per cent in 1981 to 2.5 per cent in 1991<sup>156</sup>. One conclusion must be that for a separation of drug markets to work and any escalation to end then a controlled and monitored distribution of the drugs provides a better framework for success.



6.9.20 *Summary*: The potential value of cannabis and cannabinoids as a substitute drug in the treatment of opiate and alcohol addiction has been reported since the 19th Century, and is briefly noted in the recent BMA report. There appears to be a growing body of scientific evidence suggesting a potential role for cannabinoids in alleviating opiate withdrawal symptoms, and there have been a number of anecdotal reports of effective substitution of alcohol with cannabis, but few controlled clinical studies have been performed.

6.9.21 There is increasing but conflicting anecdotal evidence of efficacy as an adjunctive drug or as a substitute for opiates. The evidence cannot be regarded as conclusive, but the common modality suggested by Di Chiara et al offers a theoretical basis both for common analgesic activity of THC and morphine, and for attenuation of opiate withdrawal symptoms by cannabis. There would appear to be sufficient evidence to justify further research in this area.

## 6.10 *Uses of cannabis in treatment of alcoholism*

6.10.1 Mattison<sup>157</sup> cited Dr Ansle's (*Materia Medica* 2nd vol) as recommending use of cannabis for the relief of pains from chronic alcohol taking, and quoted several other physicians reporting efficacy in relieving delirium tremens. J. Russell Reynolds, Royal Physician, found treatment of alcoholic delirium with cannabis to be "very uncertain, but occasionally useful"<sup>158</sup>. Allentuck, author of the medical aspect of the 1944 La Guardia report on marijuana, reported that preliminary experiments on treatment of alcoholism in private patients were sufficiently encouraging to merit further investigation<sup>159</sup>.

6.10.2 In the 1960s the use of marijuana in the USA was the focus of a number of studies reviewed by Kaplan<sup>160</sup>. Blum found that 54 per cent of regular (weekly) and 89 per cent of daily marijuana users reported decreased alcohol consumption<sup>161</sup>, Tart & Klein<sup>162</sup> found a general reduction in student alcohol use following increased marijuana use. A study of Stanford University students found three per cent of marijuana users had increased liquor consumption compared to 32 per cent who had decreased, and Halleck<sup>163</sup> reported that cases of alcohol poisoning were increasingly rare, attributing this to the rise in marijuana use on campus. Downs<sup>164</sup> reported sharp reductions of alcohol intake in marijuana users, resulting in improved physical and mental health. Kaplan also considered reduced availability of marijuana to risk wider use of more dangerous drugs and alcohol. The potential increase of alcohol use arising from a proposed ban on cannabis in India was also one of the reasons used by the British Raj to oppose any introduction of prohibition in the Indian Hemp Drugs Commission report of 1894.

6.10.3 One widely-quoted paper by Mikuriya<sup>165</sup> reported successful self-treatment of withdrawal symptoms of alcohol and subsequent rehabilitation in a 49 year old woman with a 35 year history of severe alcoholism. He considered that for selected alcoholics the substitution of smoked cannabis for alcohol may be of marked rehabilitative value, the absence of irritability of gastrointestinal symptoms on withdrawal to assist in rehabilitation, and that further clinical trials would be warranted. Scher<sup>166</sup> also proposed clinical trials following his clinical experience that marijuana and alcohol were mutually exclusive agents, and that considerably less of each would be used when used together than when each was used alone. Rosenberg et al<sup>167</sup> found cannabis not to be particularly effective, alone or in conjunction with disulfiram (antabuse), in inducing alcoholics to enter or remain in treatment. However the experiment used single doses of cannabis (approx 20mg THC) and the findings would be of little relevance to daily cannabis users. Jones<sup>168</sup> found evidence suggesting some cross-tolerance between the effects of alcohol and cannabis, later confirmed by Hollister<sup>169</sup>.

6.10.4 Thompson and Proctor<sup>170</sup> found that 59 alcoholic patients out of 70 had their withdrawal symptoms alleviated by administration of pyrahexyl, a synthetic cannabinoid, 11 patients showed no improvement.

6.10.5 Brecher<sup>171</sup> reviewing the issue in 1972, considered the evidence to suggest that marijuana smoking tended to replace alcohol drinking, but also noted then recent increases in popularity of alcoholic drinks among US youth. He quoted several individual testimonials, including Professor Lindesmith, Indiana University sociologist, from 1968:

"... some pot smokers, both old and young, have developed an aversion to alcohol, regarding it as a debasing and degrading drug ... Some of these people were heavy users of alcohol before they tried marijuana and feel that the latter saved them from becoming alcoholics."

6.10.6 More recently, Bello<sup>172</sup> reported the effect of increased cannabis use on reducing alcohol consumption among severe alcoholics, considering cannabis to "ease the symptoms of withdrawal", although one habit was replacing another, and considered the gradual substitution of alcohol with marijuana to be of benefit to these drinkers.

6.10.7 Hoffman et al<sup>173</sup> found evidence to suggest that ethanol withdrawal symptoms are mediated by changes to NMDA (n-methyl-d-aspartate) receptor metabolism, and the BMA reported a synthetic cannabinoid<sup>174</sup> to be a potent NMDA antagonist<sup>175</sup>, which would counteract excessive NMDA-ergic activity associated with convulsive disorders<sup>176</sup>. The well-established anticonvulsant effect of cannabidiol (CBD) may offer some relief from the acute withdrawal symptoms (delirium tremens) in the most severe alcoholics.

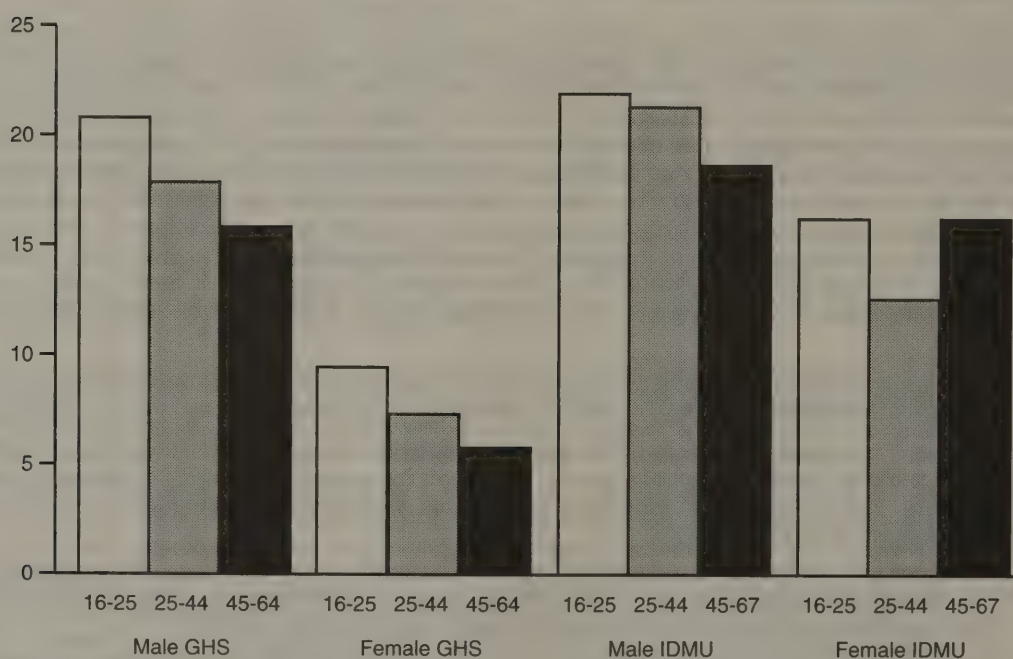
6.10.8 In a longitudinal study in Norway, Hammer and Vaglum<sup>177</sup> failed to find any evidence of increased alcohol use among those who had ceased using cannabis. Although significantly higher consumption of

alcohol was found in past cannabis users than non-users, the highest levels were found among the current cannabis users.

6.10.9 Our own research<sup>178</sup> suggests there to be more negative attitudes to alcohol among daily cannabis users than among less frequent users, although the differences in reported alcohol consumption among the different cannabis-using groups failed to achieve statistical significance.

- (a) There were weak negative correlations between cannabis use indices and alcohol frequency-of-use and spending data.
- (b) The amount of cannabis used per month correlated negatively with all alcohol use indices, suggesting that heavier cannabis users may use alcohol slightly less frequently, drink and spend less, and have more negative attitudes to alcohol.
- (c) Respondents as a whole showed a lower proportion of abstainers, and a higher proportion of heavy drinkers (especially among women) than those of comparable age groups as quoted by Alcohol Concern<sup>179</sup>. Abstainers from alcohol may be less likely to have tried illicit drugs. The abstention rate was three times higher among women over 25 than among the younger women. None of these statistics give any indication as to whether alcohol consumption had changed following use of cannabis.
- (d) It is possible to compare the alcohol consumption of IDMU respondents with that of a comparable age cohort from the 1996-97 General Household Survey data<sup>180</sup>. For each age group the consumption of respondents was higher than the GHS "control" sample. This difference was increasingly marked in the older age groups, although overall use in each sample declined with age. There was a notable sex difference, with female IDMU respondents drinking twice as much as the national average, whereas male respondents drank one third more. This difference was more marked at younger and older age groups (See fig 2 below).

**Units of alcohol consumed per week by age and sex**  
**Comparison of IDMU Drug User and General Household surveys**



6.10.10 The dataset for the "45-67" IDMU age cohort was considerably smaller (57 male, 28 female) than for the other age groups, and these results should be interpreted with caution. The "Regular Users" population may indicate a lower rate of abstentionism, and slightly higher numbers of heavy drinkers, among the cannabis-users than in the population as a whole. These results may be attributable to the greater "deviance" of older drug users, particularly women, from the norms of their contemporaries, compared to the "normalisation" of drug use among the young.

6.10.11 There is some historical and scientific evidence to suggest cannabis or cannabinoids may have potential therapeutic uses in the treatment of alcoholism, particularly during the acute withdrawal stage. However, any such use, or use as a drug of substitution, could not become generally accepted within medical opinion without properly conducted research including clinical trials.



## SECTION 7. LEGALISING MEDICAL USE—THE CALIFORNIAN EXPERIENCE

7.1 *Brief history of reform*

7.1.1 In 1996 the state of California passed the Compassionate Use Act, (Health and Safety Code 1132.5). “To ensure that seriously ill Californians have the right to obtain and use marijuana for medical purposes where the medical use has been recommended by a physician”. This had been proposed by petition of over 20,000 people, and passed with 56 per cent of the state vote, in a referendum known as Proposition 215, or The Medical Use of Marijuana Initiative. The state of Arizona passed a similar law at the same time.

7.1.2 The code provides that State possession and cultivation laws “shall not apply to a patient, or a patient’s primary care giver, who possesses or cultivates marijuana for the personal medical purposes of the patient, upon the written or oral recommendation or approval of a physician”.

7.1.3 The law is specifically about raw herbal cannabis (marijuana). It does not appear to apply to THC or other extracts or synthetics. (dronabinol is available on prescription). Permitting cultivation potentially removed the problems of obtaining supplies. Permitting the assistance of a “primary caregiver” was an essential element, allowing access to the drug for people too sick to grow or obtain it, or who lived in inconvenient locations such as nursing homes.

7.1.4 Among members of Cannabis Buyers Clubs, the most common reasons given for medical use included anorexia, nausea, vomiting, insomnia, depression, anxiety/panic attacks, arthritis and other pain relief, AIDS related illnesses, muscle spasm, and harm reduction (reducing or controlling other drug or alcohol abuse)<sup>181</sup>.

7.1.5 Briefings to District Attorneys, police, and doctors suggested that a doctor must have approved the marijuana use, but need not have issued a formal written prescription. The amount must be appropriate to the patient’s medical needs—possession for sale, and sale, remain crimes in any circumstance. In Californian law, possession of under 28.5 grams (1oz) is usually deemed to be for personal use, and dealt with by a written citation and confiscation, which would still apply in all non-medical cases.

7.1.6 Codes of practice were produced in several areas for police, doctors, and care givers. In February 1997 the State Attorney General (who campaigned against the Proposition) issued detailed guidelines<sup>182</sup> for law enforcement officials, on enforcing laws against marijuana in the light of the changes. This suggested that suspects claiming medical necessity would have to be:

- (i) California residents who were seriously ill,
- (ii) had been examined by a doctor, who had determined that their health would benefit from marijuana use,
- (iii) should not be engaged in conduct that endangers others, such as driving a car,
- (iv) should not be involved in any diversion for non-medical purposes, such as furnishing to friends or using strictly for recreation, and
- (v) should not possess or grow more than needed for personal medical use.—It was suggested that one plant would produce one pound of marijuana, or 1,000 “joints”, and that therefore “one can argue that two or more plants would be cultivation of more than necessary for personal medical use.” Alternatively, possession of more than 28.5 grams might be more than personally medically necessary.
- (vi) If a suspect claimed to be a primary caregiver they must have been specifically designated by the patient, in advance, and have specific knowledge of the doctor’s recommendation.

7.1.7 Some police forces issued medical marijuana user photo-ID cards to patients after checking their doctors’ recommendations; to avoid them having to prove their case repeatedly.

7.1.8 Also in February, the San Francisco Department of Public Health issued guidelines for dispensing medical marijuana<sup>183</sup>, including standard forms for doctors’ recommendations and nominating “primary care-givers”, and a code of practice for dispensing centres, mostly concerned with very careful record-keeping.

7.1.9 In July 1998 Oakland City Council adopted a limit of 24oz(1½lb or 680g), or 100 plants, on the amount of marijuana to be allowed for medicinal use by any one patient<sup>184</sup>. This was based on the amount needed for three months supply (a typical growth cycle), by patients in receipt of medicinal marijuana in the wake of the Randall case<sup>185</sup> (see below), smoking 10 pure cannabis cigarettes per day each containing 0.9g of cannabis with 2 per cent THC.

7.2 *U.S. Government and medical marijuana*

7.2.1 The US Federal government opposed Proposition 215 before and after it was voted into law, arguing that it was against national and international law to allow possession or cultivation of cannabis for any purpose. This opinion has been challenged in the US courts on several grounds, and is currently being disputed. It seems very likely that in the long term Federal law will override the State legislation, and the Compassionate Use Act will be overturned.

7.2.2 All uses of cannabis were effectively banned in the USA from 1937, under the Marijuana Tax Act. The Controlled Substances Act 1972 is similar in outline to British drug control laws; it places cannabis and its derivatives in Schedule I, among the drugs which “have no accepted medical use in the United States and have a high abuse potential”. There are five schedules, substances in the lowest can be distributed without a prescription but only by a pharmacist.

7.2.3 There have been occasional attempts and recommendations to re-introduce the medical use of marijuana, eg California Research Advisory Panel 1970, compassionate Investigative New Drug status until 1991, numerous local and federal court cases. In 1977, a glaucoma sufferer, Robert Randall, was acquitted of growing cannabis plants, on appeal, on the defence of medical necessity. He successfully petitioned the federal government to provide him with legal marijuana to preserve his eyesight. He was eventually entered on a research project, and was provided with a regular supply of government-grown, ready-rolled, neat marijuana “joints” of a standardised strength from the National Institute on Drug Abuse’s research centre. He is still smoking them regularly to this day. Several other individuals later obtained supplies from the government, for various ailments, in each case after long court cases and negotiations. The requirement in general was to prove medical needs which could not satisfactorily be met by other drugs, or by synthetic cannabinoids. The Randall case established a precedent that herbal cannabis, smoked, could be more effective in treating some conditions than extracts or cannabinoids.

7.2.4 The same ready-made “joints” were available to suitably qualified researchers in the US from the early 1970s on. The synthetic cannabinoid Marinol (dronabinol) was made available for research and a limited range of prescriptions in 1985. Other cannabinoids have been available for research through NIDA. In 1988, the Drug Enforcement Administration’s chief administrative law judge recommended reclassifying marijuana so that it could be prescribed, but no action was taken.

### 7.3 *Distributing medical cannabis—Buyers Clubs*

7.3.1 The validity of sales by non-profit clubs, often co-operatives, acting as “primary care givers” or cannabis dispensaries, was unclear in the law. Several were shut, and some re-opened, in legal actions in the early months after the Act was passed. In March 1997 the Superior Court in San Francisco ruled that such a club could be legal, if members had each designated the club as primary care giver, it was non-profit, each person treated had a doctor’s recommendation, and they kept detailed records of what was dispensed to whom. This was overturned on appeal by Federal authorities, and at the end of May 1998 several clubs were closed down by court orders. Others have shut voluntarily pending legal appeals. At the same time the State Attorney General has brought another case that the clubs do not qualify as “primary care givers” under the Act.

7.3.2 Some of the cannabis buyers clubs had existed before the law was passed, and played a large part in the campaign for Proposition 215. Several were linked with existing AIDS and cancer-victim activist groups. There were over 30 such clubs in early 1998, the largest with over 9,000 members. Many people who were too sick to obtain or grow their own claimed that the clubs were their only potential source of marijuana. Cannabis was grown by club members, and sold in small amounts to other members, without profit, as smokeable marijuana, powdered in capsules, tea, or cookies, usually but not always for the patient to take away.

7.3.3 Two ethnographers had a Drug Policy Foundation research grant to analyse 12,000 intake forms from one buyers club, with the goal of determining the distribution of disease categories and demographic characteristics of members. However, the club was raided in March 1996, temporarily shut down, and the records remain sealed. Instead, the researchers investigated the way members used the club, and the impact of its closing, by interviews and observations<sup>186</sup>. Respondents reported highly positive health benefits from marijuana itself, and even greater benefits from the social aspects of the clubs, which they described as providing important emotional support groups, of therapeutic value to the sick and terminally ill.

7.3.4 The position of individuals or their care-givers who can provide their own medical marijuana, remains unclear: They are not breaking California laws at present, but they are breaking Federal law.

7.3.5 A document released by the California Medical Association in January 1998 invoked the Federal law and told physicians in the state to steer clear of prescribing marijuana. The federal “Drugs Czar” had suggested publicly that they might lose their licences to prescribe common drugs if they co-operated with proposition 215.

7.3.6 In late May 1998, the Mayor, City Supervisors, District Attorney and Public Health Director of San Francisco were proposing a new bill to establish a model for the distribution of marijuana to medically ill patients, who would no longer be able to obtain supplies when the clubs were banned<sup>187</sup>. They felt that without the co-operation of most doctors, or the club distribution network, the law would be almost impossible to implement even if it was legitimate under federal law. At one point it was seriously suggested by these officials that the City and County public health service should grow and distribute the marijuana, or make arrangements with existing medical clinics to do so. Another suggestion was that police could provide confiscated marijuana to qualified patients.

7.3.6 At the same time, police, prosecutors and lawmakers from all over California met in Sacramento to consider strategies for fully implementing Proposition 215. They concluded that it would be impossible



without the co-operation of the federal government, which they were very unlikely to get. Federal agency representatives did not attend.

7.3.6 Many of the participants, including the California Medical Association, concluded that a necessary first step would be to persuade the federal government to reclassify marijuana from Schedule I to Schedule II. A Schedule II designation would allow physicians to directly prescribe marijuana to patients, removing the need for private dispensaries.

#### 7.4 Problems and benefits of the Californian model

7.4.1 The fact that Proposition 215 got on the ballot at all, and was then passed by 56 per cent of the vote, indicates a wide public acceptance of the use of marijuana for medical purposes. It is an issue in this year's local elections for Governor, State Attorney-General, and Mayor of San Francisco, with most candidates supporting some level of medical use, even when they are hostile to this particular way of providing it. In Oregon a similar referendum has qualified for the ballot, in Nevada a similar petition failed to achieve the required number of signatures in two small rural districts.

7.4.2 The Act supports medical use of herbal cannabis (marijuana). It does not affect the possibility of using derivatives or synthetic cannabinoids if they are appropriate. This recognises that marijuana is by far the more easily available, already being used illegally in some cases, and cheaper. There is extensive anecdotal evidence that it is more effective in some illnesses. The effects of marijuana are undoubtedly different from those of any single derivative and there seems no reason to doubt the views expressed by individual patients that smoked cannabis is more effective and easier to control. Similar control might be achieved by inhalers or other routes using synthetic or extracted cannabinoids.

7.4.3 The Act supports cultivation for personal medical use. This is the most obvious way to provide cannabis, a common plant which can be grown easily almost anywhere. It avoids patients having to add to the criminal economy, and is cheaper for them. However, it provides uncertain doses of a complex drug with variable effects. This could be mitigated in monitored, larger scale, or collective production: fine quality control on plant products, though perhaps not to pharmacologists' standards, is well established in the food, beverage and tobacco industries.

7.4.4 'Primary care givers' were authorised to possess or grow cannabis for others' personal medical use. This made access to the drug possible for people too sick to grow or go out and get their own, or who lived where home cultivation was impractical, such as in hospices.

7.4.5 Methods of certifying and monitoring medical use were put in place. Police and prosecutors' responses to the legal change were devised. No doubt they will be extensively tested in the local courts.

7.4.6 Only small numbers of patients have the wherewithal, patience, and knowledge to regularly grow enough of their own cannabis plants, of the right quality, for their medical needs. In some cases pollen or moulds might exacerbate medical problems. Buying from the illegal market offers risks of arrest (though not prosecution), lack of availability when needed, and of poor quality and prices. Distribution from police seizures, or cultivation and distribution by medical services, have been suggested but met legal, political, moral and practical difficulties.

7.4.7 The co-operative Buyers Clubs offered one workable method of producing and distributing enough marijuana for medical needs, without a surplus available for diversion. They could also have been used for quality and dosage control. Their legal position was at best ambiguous. Their development was *ad hoc* and in some cases illegal. As well as extreme hostility by Federal and some State law officials, they were damaged by personality politics and, especially, by over enthusiastic promotion by some advocates of legal marijuana. Nevertheless, the clubs were so successful that the State authorities have had to consider taking over their role now that they have been shut down.

## SECTION 8. TREATMENT OF "MEDICINAL" CANNABIS USERS BY THE UK CRIMINAL COURTS

### 8.1 Overview

8.1.1 In consideration of the illegal nature of cannabis for many patients already self-medicating with the drug, the BMA recommended in November 1997:

"While research is underway, police, the courts and other prosecuting authorities should be aware of the medicinal reasons for the unlawful use of cannabis by those suffering from certain medical conditions for whom other drugs have proved ineffective."

8.1.2 I am not aware of any separate notification of "medicinal" defences to the Home Office or Scottish Office allowing any national statistics to be determined. We are drawing on three main sources for information on how the courts are currently responding to medicinal uses defences:

- (1) Reports from survey respondents citing medicinal reasons as a motivation for use, who have been "busted", giving outcomes where stated.

- (2) Previous cases involving medicinal use, outcomes where known.
- (3) Press and internet reports.

## 8.2 IDMU user surveys

8.2.1 In the combined 1994–98 sample, some 70 respondents reported medicinal use as a major motivation for using cannabis. Of these, 27 (39 per cent) had been “busted” for cannabis offences.

8.2.2 Table 6 below presents, where stated, the results of prosecutions, and conditions involved, for respondents indicating both medicinal use and a cannabis “bust”. The quantities of drugs involved in each case and whether medical use was raised during proceedings is not known.

8.2.3 The most common disposal was by way of fine, and I note that the heaviest fines levied were against users whose medicinal need was vague or questionable. However the 18 months sentence imposed for simple possession where cannabis was used for pain in arthritis might not suggest a lenient attitude by the courts.

8.2.4 The proportion cautioned at 22 per cent was well below the national average, and the “bust rate” for “medicinal” was about 50 per cent higher than the rest of the sample. These may reflect institutional scepticism at claims of therapeutic benefit, or merely be a function of the higher average age of this subgroup of users, leading to an increased risk of detection, and a perhaps greater reluctance on the part of the police to caution more mature offenders compared to younger people.

**Table 6**

### IDMU DRUG USER SURVEYS 1994–98 OUTCOMES OF CRIMINAL PROSECUTIONS REPORTED AMONG MEDICINAL USERS WHO REPORTED ONE OR MORE CANNABIS “BUSTS”

| <i>Sentence Type</i>    | <i>n</i> | <i>%</i> | <i>Offence/comments</i>   |
|-------------------------|----------|----------|---|
| Total Respondents       | 27       | 100      | 0.97 per cent of total sample, 39 per cent of “medicinal” users   |
| Cautioned               | 6        | 22       | 5 x possession only (depression/asthma; depression/stress/pain; stroke victim (carer); muscle relaxant; back pain/muscle relaxant)<br>1x possession + production  |
| Conditional Discharge   | 3        | 11       | 2 x possession, (asthma/pain/stress; general health)<br>1 x production and possession (not stated)  |
| Fine                    | 12       | 44       | £25 (possession cannabis + amphet—sleep/pain),<br>£30 (possession—asthma/pain/stress),<br>£30 (possession—not stated),<br>£50 (import—arthritis/pain),<br>£60 (possession/production—pain),<br>£65 (possession—alcoholism/depression),<br>£75 (importation—“severe illness”),<br>£80 (possession with intent—pain/asthma),<br>£125 (production/possession—depression),<br>£200 (possession—“health”),<br>£650 (possession, production, possession with intent—insomnia),<br>Amount unknown (possession—pain/arthritis). |
| Community Service Order | 2        | 7        | 180 hours (possession—back pain/insomnia)<br>80 hours (pain/asthma)   |
| Suspended Sentence      | 2        | 7        | 4 months suspended 2 years (possession with intent—migraine)<br>Unknown (possession with intent—pain/asthma)  |
| Immediate custody       | 2        | 7        | 9 months (possession 1967—glaucoma/asthma)<br>18 months (possession—pain/arthritis)   |
| Unknown/Other outcome   | 3        | 11       | Result unknown (condition not stated),<br>Result unknown (“asthma”),<br>“Didn’t get caught” (“incurable disease”).  |



8.3 *IDMU case records*

8.3.1 The main service provided by IDMU is expert evidence to the criminal courts on most aspects of drug misuse, including comment on consumption patterns, valuations, effects, paraphernalia and yields of cannabis cultivation systems. Just under 10 per cent of referrals to our agency involve a claim of medicinal cannabis use, where comment is sought on scientific and other evidence as to the potential therapeutic use in specific conditions. In order to filter out bogus medical defences, the instructing solicitor is required to provide evidence of a “relevant medical condition” before any comment on medicinal uses can be offered. The conditions encountered in cases and referrals to date are summarised below.

**Table 7.1**  
**IDMU MEDICINAL CANNABIS CASES**  
**1—CONDITIONS ENCOUNTERED IN REFERRALS**

| <i>Condition</i>               | <i>n</i> | <i>%</i> |
|--------------------------------|----------|----------|
| Pain Relief                    | 24       | 60       |
| Addiction to alcohol/heroin    | 4        | 10       |
| Spasm/Cerebral palsy           | 3        | 7.5      |
| Asthma                         | 3        | 7.5      |
| Insomnia                       | 3        | 7.5      |
| Stress relief                  | 2        | 5        |
| Antidepressant                 | 2        | 5        |
| Epilepsy                       | 2        | 5        |
| Multiple Sclerosis             | 2        | 5        |
| Hintingdon’s Chorea            | 1        | 2.5      |
| HIV                            | 1        | 2.5      |
| Condition not stated           | 3        | 7.5      |
| Total cases                    | 40       | 100      |
| (8.5% of total IDMU enquiries) |          |          |

8.3.2 The vast majority of cases have involved pain relief and/or spinal injury, there have been a limited number of other conditions. Several cases have involved more than one condition and thus columns cannot be added together to produce totals.

8.3.2 In most of our cases the defendant is charged with possession of cannabis or cannabis resin with intent to supply, including a substantial number of cultivation cases. The nature of our service inevitably over represents the borderline between personal use and supply—defendants who are cautioned do not need expert evidence. The medicinal issue is commonly raised as an explanation of amounts possessed, or used as mitigation during sentencing where there is a guilty plea to possession and/or production/cultivation.

8.3.5 Medicinal evidence, where substantiated, is frequently accepted by the court or the Crown. The evidence commonly results in a plea bargain and non-custodial sentence, although “possession with intent” charges are commonly pursued on users with more than a few days supply, or more than a handful of cannabis plants. Although the courts can show compassion in some cases, there is considerable variation in outcomes and sentencing for similar offences. The outcome and sentencing is very much affected by the attitudes of individual judges.

8.3.6 In my experience, juries are more likely to acquit defendants in borderline cases or even with larger quantities where there is convincing medical evidence, given similar circumstances concerning paraphernalia.

**Table 7.2**  
**IDMU MEDICINAL CANNABIS CASES**  
**2—DISPOSAL OF CASES**

| <i>Disposals</i>                        | <i>Number</i> | <i>% of Cases</i> | <i>Comments</i>   |
|---|---------------|-------------------|---|
| Case not pursued beyond initial enquiry | 6             | 15                | Legal aid not awarded or other expert used  |
| Supply charges withdrawn                | 8             | 20                | 300 plants (pain/arthritis)<br>2.3kg outdoor homegrown (pain)<br>30 plants (alcoholism).<br>20 plants (HIV),<br>120 plants (pain),<br>150 plants (pain/oral use), |

| <i>Disposals</i>                                   | <i>Number</i> | <i>% of Cases</i> | <i>Comments</i>   |
|--|---------------|-------------------|---|
| Supply dismissed/<br>no case to answer             | 4             | 7.5               | 450g resin (opiate withdrawal),<br>14 plants (pain).  |
| Acquitted by jury<br>of supply charges             | 6             | 15                | 6 large plants (spinal injury),<br>300g "homegrown" (Asthma),<br>2oz Resin (spinal injury),<br>40 plants (pain).  |
| Acquitted by jury<br>of all charges<br>(necessity) | 2             | 5                 | 85 plants (spinal injury),<br>8oz resin + 80 plants (epilepsy),<br>97g resin (arthritis),<br>82 plants (stress relief),<br>247g resin (Pain),<br>100g herbal (pain).                                      |
| Plead guilty (inc<br>production/social<br>supply)  | 5             | 12.5              | 1. MS—possession/supply of<br>spouse—other expert used,<br>2. Pain/spinal injury—18 plants,<br>—judge held necessity to apply<br>where there is "no alternative way<br>to avoid death or serious injury". |
| Convicted by<br>Jury/Sheriff                       | 7             | 17.5              | 2,000 small plants (pain),<br>500g herbal (asthma),<br>2oz resin (pain/asthma)  |
| Hung juries/<br>retrials                           | 2             | 5                 | 50 plants (epilepsy),<br>200g oil (pain/opiate addiction),<br>4oz resin (pain),<br>8oz resin (pain),<br>225 plants (alcoholism),<br>85 plants (pain),<br>120 plants (pain/alcohol).                       |
| Live cases<br>awaiting trial                       | 4             | 10                | 97g resin (spinal injury—acq),<br>120 plants (pain/alcohol—con)   |
| Outcome/Sentence<br>unknown                        | 9             | 22.5              |   |
| Total cases  | 40            | 100               | 8.5% of total IDMU enquiries.   |

8.3.7 Some judges appear more willing to forego custodial sentences where there is persuasive evidence of medicinal use. Other judges take a harder line, particularly in Scotland where custodial sentences are common for minor cultivation offences even where supply charges have been discontinued, and in a case in Northampton where the defendant's acquittal by a jury on a charge of possession of 97g resin with intent (following an initial hung jury and retrial), was followed by a large fine (£1,000) on the charge of simple possession, to which the defendant had already pleaded guilty.

Table 7.3

IDMU MEDICINAL CANNABIS CASES  
3—SENTENCING OF OFFENDERS

| <i>Sentence</i>                    | <i>Number</i> | <i>% of cases</i> | <i>Comments</i>   |
|------------------------------------|---------------|-------------------|---|
| Conditional/Absolute<br>discharges | 5             | 12.5              | 2.3kg homegrown (pain)<br>300 plants (pain)<br>80 plants (epilepsy)<br>2 x spouses of accused growers   |
| Probation                          | 2             | 5                 | Unknown—247g resin possession only<br>2 years—production 30 plants (alcoholism)   |
| Fine                               | 4             | 10                | Costs only—possession 8oz resin/production 80 plants<br>following supply acquittal (epilepsy)<br>£1,000 for possession of 97g resin following jury acquittal on<br>intent charge (pain)<br>£300 for production of 85 plants after jury acquittal on intent<br>(pain/spinal injury)<br>£200 plus costs for production 6 plants after supply<br>dismissed by Sheriff (pain/spinal injury) |



| <i>Sentence</i>                 | <i>Number</i> | <i>% of cases</i> | <i>Comments</i>   |
|---------------------------------|---------------|-------------------|---|
| Suspended sentences             | 3             | 7.5               | 2,000 cuttings (pain)<br>Social supply of resin (pain)<br>20 plants (HIV)   |
| Community Service Order         | 3             | 7.5               | 50 hours—30g herbal (pain/insomnia)<br>150 hours—14 plants (pain)<br>Unknown—30 plants (alcoholism)   |
| Immediate custody               | 7             | 17.5              | 3 years—cultivation 220 plants (alcoholism)<br>12 months—40 plants with intent (pain)<br>9 months—small cupboard production only (pain)<br>9 months—40 plants in greenhouse—production only (pain/spinal injury)<br>9 months—80 plants (pain)<br>6 months—social supply 3oz resin<br>Unknown—50 plants (epilepsy) |
| Live cases still awaiting trial | 4             | 10                |   |
| Result/Sentence unknown         | 9             | 22.5              |   |
| Total cases                     | 40            | 100               | 8.5% of total IDMU enquiries  |

#### 8.4 *Press and Internet Reports*

8.4.1 It is easy to point to some of the recent sentencing of medicinal users in the UK as indications of compassion and understanding entering the judiciary with regard to such cases. However, within the context of a chronically or terminally ill person self-medicating, one should not underestimate the psychological and physiological damage caused by the stress of a police raid, arrest and subsequent court case, regardless of outcome. When cases take a long time to come to court the stress and foreboding are prolonged and, since the medicine which they had relied on is no longer available to them, in such cases the patient is probably more vulnerable and less able to cope with their illness than before.

8.4.2 The stress may even be exacerbated by the fact that there is even less consistency in UK sentences for medicinal cannabis use than there is for cases involving recreational use. In consequence the patients have very little certainty in approaching their trial as to what sentence they may receive or, indeed, what plea they may be able to enter.

8.4.3 In June 1998 Colin Davies, a former joiner who had suffered serious spinal injuries falling 60 feet from a bridge in 1994, was acquitted by a jury in Manchester Crown Court of charges of cultivation after representing himself with a defence of necessity<sup>188</sup>.

8.4.4 However, at Maidstone Crown Court in 1997 Andrew Betts, Britain's only sufferer of Familial Mediterranean Fever, an inherited and non-fatal condition, was conditionally discharged for two years after appearing on charges of cultivating 45 cannabis plants at his home. Despite having been the sole subject of licensed cannabis tests at Hammersmith Hospital in west London, which enabled him to halve his daily intake of morphine and left him no longer clinically depressed, Betts was forced to plead guilty after Mr Recorder Peter Morgan ruled that his defence of necessity or duress could not be put before a jury<sup>189</sup>.

8.4.5 In 1998 Margaret Startin, a mother of two who cares for her chronically arthritic 54-year-old husband, was fined after police raided her home in Cannock and found plants growing under lights in the loft. At Stafford Crown Court she admitted possessing cannabis with intent to supply and was fined £500 and ordered to pay £1,123 costs. Her husband was fined £250 after he admitted growing the drug<sup>190</sup>.

8.4.6 Those who have been driven to use cannabis because they see it as the only efficacious treatment for their illness seem likely to continue to use it if they can despite the legal consequences.

8.4.7 In March Richard Gifford, a liver transplant patient and former Royal Engineer, received a two year conditional discharge for growing 12 cannabis plants in his back garden. Despite this he pledged to carry on smoking the drug: "While I am still alive, I intend to carry on using it," he said<sup>191</sup>.

8.4.8 Davies, too, stated that he would not stop medicating himself: "I will carry on smoking cannabis," he was quoted as saying. "It helps the terrible pain I get from my injuries. I feel vindicated that the jury has listened to me." This prompts the question of the validity or purpose of repeating prosecutions of medicinal cannabis users with no likelihood of forcing them to cease their use of the drug.

8.4.9 One aspect of note in the medical cases reported in the UK press is that they are primarily involved with patients who grow their own cannabis. This may be because it is easier to conceal the drug itself as a small package of herbal cannabis or cannabis resin than to successfully hide the cultivation of a number of plants for a period of months. However, it may indicate that medicinal cannabis users are simply more likely to grow their own plants. There are many reasons for medicinal users to do so. They can be guaranteed of

the purity of the drugs they use. They can avoid contact with dealers and the associated drugs scene. They can afford to medicate themselves as and when needed at a fraction of the cost of commercially available cannabis. They can avoid having to search for sources of their medication. All these might be seen as aspects of harm reduction in the case of non-recreational drug users.

8.4.10 It is fairly clear that many of those prosecuted feel it to be iniquitous that it is through their determination to avoid being involved in a drugs subculture or to buy in to the criminal industry they have been branded as criminals.

8.4.12 Colin Davies is quoted as saying “I read about cannabis as a relief from pain and I actually went out and bought some off the streets . . . I did not like having to do that so I decided to have a go at growing some for my own use on my own property. I did it behind my own front door, there is no interference with anyone else. I now find myself here and I feel terrible”.

8.4.13 By being forced to relinquish their own supply users are forced into the very behaviour that their cultivation of cannabis was intended to avoid. In the case of Richard Gifford the report stated that he had “been buying it on the streets since the police cut down his 12 eight foot plants.”.

### Memorandum by the Institute for the Study of Drug Dependence

1. What follows is based on ISDD’s forthcoming update of its *Cannabis Drug Notes*. This is not original research but a considered review of what is known. The source of all such material is ISDD’s comprehensive library on all aspects of drugs. We have also identified those areas in which the existing research provides firm evidence and those in which more research would be required before conclusions can be drawn.

What are the physiological effects (immediate, long-term and cumulative) of taking cannabis, in its various forms?

[The Department of Health has unpublished reports in this area.]

There is a firm evidence base on the short-term effects of cannabis use.

2. The effects generally start a few minutes after smoking, and may last up to one hour with low doses and for up to two or three hours with higher doses. Cannabis causes a number of noticeable but usually mild physical effects, including increased pulse rate and later decreased blood pressure (so those with heart complaints may be at special risk), bloodshot eyes, dry mouth, increased appetite, mild pain reduction and occasional dizziness.

3. Cannabis has been shown in laboratory conditions to have detrimental effects on physical coordination, reaction time, memory and the ability to learn complex tasks. This has been shown to reduce task performance, in particular operating machinery and being in charge of a vehicle or aircraft. There may be impairment of short-term memory (ie recall of the events of the last few minutes or seconds) and of the ability to drive or perform other intellectual or manual tasks. Effects such as these have been shown to persist up to 24 hours after use.

4. Statistics from the Department of Environment, Transport and the Regions, have shown that 10 per cent of drivers involved in road accidents had traces of cannabis in their blood. This may, however, be more an indication of the numbers of people in the population who have used cannabis than of the effects the drug has on driving; cannabis traces in the blood do not mean that an individual is intoxicated. Cannabis can remain stored in small amounts in the body’s fat for up to 30 days after use. There is no indication that such deposits affect performance in any way.

The evidence for the long-term effects is less robust, and more research is needed. A great deal of cannabis research has come under methodological criticism because researchers have either failed to control for social and individual differences, have a small or only anecdotal sample base, or have worked with preconceptions as to the possible outcomes of the research. The University of Mississippi has an ongoing project to collect and collate into bibliographies all the world’s literature on cannabis including the many thousands of animal studies. In general, laboratory experiments with animals suggest that cannabis may be damaging in a number of respects.

5. As far as physical damage to health is concerned, it has been shown that (as with tobacco smoke) frequent inhalation of cannabis smoke over a period of years can exacerbate bronchitis and other respiratory disorders, and can also cause cancer of the lung and other parts of the upper digestive tract—smoked cannabis contains higher concentrations of potentially carcinogenic tar and toxins.

6. Cannabis use has also been shown to weaken the lung’s ability to fight infection. Tests have indicated that cannabinoids act as immunomodulators, which, in sufficient doses, can go on to impair the functioning of the lungs’ immune cells. Most of the effects are small and reversible, suggesting that only in very heavy smokers may any degree of mutation be significant. Large population studies have however shown that incidences of lung infections are somewhat more common in cannabis smokers than in other smokers.



7. Regular, frequent cannabis use during pregnancy increases the risk of premature birth with its attendant complications such as shorter baby length, lighter birth weight, and shorter gestation periods. Consequences such as these have been likened to those associated with tobacco smoking, and are linked possibly to foetal hypoxia—insufficient oxygen supply to growing tissue. However, results are conflicting and it is not apparent whether foetal development is affected by cannabis use or is concomitant with other factors such as the use of other drugs, poverty, and/or particular lifestyles. Some mothers who use cannabis very heavily prior to delivery have given birth to babies who temporarily suffer tremor and distress and are easily startled.

What are the psychological effects?

[The Department of Health has unpublished reports in this area.]

8. At usual doses, the psychological effects of cannabis are subtle and hard to classify. The combined effects of the cannabinoids are similar to those produced by alcohol, tranquillisers, opiates, and at stronger doses, hallucinogenic drugs like LSD. The drug has a mildly sedative and euphoric effect which seems to increase the extent to which a person is (or allows themselves to be) open to external influences (“suggestibility”). With higher doses, there may be perceptual distortions, forgetfulness and confusion, and varying degrees of temporary distress, particularly if the user is already anxious or depressed.

As with physiological effects, the evidence base for long-term psychological effects is less robust, and more research is needed.

9. Concern has been raised that heavy cannabis use during early adolescence may have some effect on social or cognitive development. Adolescence is typically defined as a time when biological and social changes are at their most pervasive, impacting on future mental capabilities and lifestyle choices. Research in the US has shown that while cannabis use during this period can act as a weak predictor of poorer academic ability and job status, it does not predict intellectual development.

10. Much attention has been paid to the drug’s apparent tendency to precipitate a chronic lack of motivation and bouts of apathy. *Amotivational syndrome*, as it is referred to, was one of the inherent dangers highlighted in the early seventies and eighties depicting intoxicated and permanently unmotivated youth. Closer examination has found that while heavy use may be linked to some behavioural disorders, they are not long-term. Such disorders appear to be linked more to psychotic incidences triggered by the effects of cannabis.

11. Certain studies undertaken in the UK and America suggest that cannabis can worsen the condition of some schizophrenic disorders. Individuals who were otherwise reasonably well-controlled on antipsychotic drugs have reported adverse reaction to regular or even sporadic use. There is no convincing support for a separate clinical diagnosis of *cannabis psychosis*, although epidemiological research has shown a link between episodes of schizophrenia and cannabis use.

How do these effects vary with particular methods of preparation and administration?

12. When eaten or drunk, cannabis takes an hour or more to have an effect which can last 12 hours or longer. If eaten, the effects cannot be regulated as well as they can if smoked because the drug is usually taken in one go. Smoked cannabis on the other hand is usually taken in smaller, more measured doses and monitored by the user over a period of time.

To what extent is cannabis addictive?

To what extent do users develop tolerance to cannabis?

13. In a laboratory situation, where people have been exposed to high doses of cannabis every few hours for several weeks, it has been possible to produce a mild withdrawal syndrome consisting of irritability, restlessness, insomnia and decreased appetite.

14. The development of a cannabis dependency syndrome in heavy users has been observed, and is associated with an inability to control use of the drug, cognitive and motivational handicaps, lowered self-esteem and possible depression in long-term users.

15. The extent of these symptoms among users is not clear, but general consensus is that very few users experience physical dependence. Regular users can come to feel a psychological need for the drug or may rely on it as a “social lubricant”: it is not unknown for people to use cannabis so frequently that they are almost constantly under the influence.

What is the evidence that cannabis in its various forms has valuable medicinal actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?

16. Currently, prescriptions for dronabinol (an active ingredient in cannabis) and Nabilone (a synthetic form of THC) are already permitted for treatment-related nausea in cancer patients where other drugs have been less effective. The recent identification of anandamide, a cannabinoid receptor in the brain and body, has led to speculation that cannabis and some cannabinoids may be effective as treatment for a number of psychological or physical disorders.

17. Faced with such speculation, last year the BMA produced the report, *Therapeutic Uses of Cannabis*, which provides the most recent and considered UK appraisal of this issue. On the basis of a review of the literature and current practice in relation to nine medical conditions (nausea and vomiting associated with cancer chemotherapy, muscle spasticity, pain, anorexia, epilepsy, glaucoma, bronchial asthma, mood disorders and psychiatric conditions, and hypertension), the report recommends that the Misuse of Drugs Act be changed "to allow the prescription of cannabinoids to patients with particular medical conditions that are not adequately controlled by existing treatments." It also recommended that researchers, pharmaceutical companies and the Department of Health "work together to encourage properly conducted clinical trials".

On the basis of the answers to these questions,

18. How strong is the scientific evidence in favour of permitting medical use?

The current evidence base—particularly in relation to the long-term effects of the drug—is poor. The BMA report acknowledged this fact and has urged that more research should urgently be undertaken.

How strong is the scientific evidence in favour of maintaining prohibition of recreational use?

19. Science alone cannot be the determinant of a position on the law. All sorts of other considerations must be taken into account including the social and economic consequences for individuals and society of both the present law and a change in the law. These are clearly defined as outside the remit of the Committee. It is difficult to point to any law that has been made solely on the basis of science. If science alone were the arbiter, then tobacco might instantly be prohibited.

#### Memorandum by the International Drug Strategy Institute

I submit my testimony regarding the serious consequences of cannabis use. Substantiating my statements I include a bibliography which will document all of my comments as well as other effects (*not printed*).

There is no doubt that cannabis is addictive. Its addiction is insidious and difficult to treat. This issue is argued by those within the pro-marijuana movement, but amusingly many of those marijuana advocates have smoked marijuana for many years without cessation. Some tolerance develops to marijuana use, and there is evidence both in both lab animals and humans of marijuana withdrawal.

Marijuana impairs memory, concentration, and many intellectual functions. It is a major factor in trauma. Marijuana impairs many types of lung function and immunity, and it causes chronic inflammation. It appears to be the cause of certain head and neck tumors.

Marijuana has negative effects on fetuses with some of the effects being seen in three and four year olds.

While there are therapeutic benefits to be derived from various cannabinoids, there is no compelling reason to allow the smoking of an impure weed as a delivery system. Marijuana contains 488 substances with 66 cannabinoids. Delivery by smoking is difficult to standardize, and is hazardous because of the numerous effects of smoking as well as the dysphoria seen with marijuana use. No evidence exists that smoking marijuana is superior to delivery of pure THC. Research should focus on delivery systems for pure THC and other cannabinoids.

Finally, the House of Lords needs to be aware that much of the support for marijuana as a medicine and for the reduction of penalties against marijuana is driven by the well organized and well financed marijuana lobby. Many of the advocates for these positions seek to either profit from the sale of legal marijuana or seek to use it without penalties. Claims that marijuana is a harmless recreational drug are specious, and suggesting that a smoked, impure weed is medicine is irresponsible.

Eric A Voth, MD, FACP  
Chairman

25 April 1998



**Memorandum by Edward H Jurith**

I am writing to assist the committee in its inquiry into the medical uses of marijuana. I am the General Counsel to the White House Office of National Drug Control Policy (ONDCP) in Washington, and currently on sabbatical as an Atlantic Fellow in Public Policy at the University of Manchester . . .

My specific project in the United Kingdom has examined the British experience in treating heroin addiction. My research has focused on policy transfers between the United States and the United Kingdom in programs that treat chronic drug addiction. It has also been my pleasure to assist Keith Hellawell in the development of the new drug control strategy for Britain.

Before taking sabbatical last September, I was deeply involved in efforts by ONDCP to address the issue of medical marijuana, particularly the Federal government's response to the passage of ballot initiatives in the states of California and Arizona to permit the therapeutic use of cannabis.

Enclosed is a copy of the Report to the Director, National Institutes of Health, by the Ad Hoc Group Experts on the Medical Utility of Marijuana (*not printed*). This report was the result of conferences sponsored by the US National Institute on Drug Abuse (NIDA) in 1997 involving leading researchers. The panel of experts has concluded that critical questions about the therapeutic usefulness of marijuana remain largely unanswered by studies conducted to date.

The panel called for more studies to properly evaluate marijuana's medical potential in five areas: analgesia; neurological and movement disorders; nausea and vomiting associated with cancer chemotherapy; glaucoma; and as an appetite stimulant. The panel also noted that any studies of marijuana's medical potential need to consider both the short- and long-term risks associated with smoked marijuana. To address many of these health concerns the panel suggested that researchers develop alternative dosages forms, such as a smoke-free inhaled system that could deliver purer forms of THC and related cannabinoids.

ONDCP has also requested that the National Academy of Sciences conduct a major study of existing research on marijuana's potential benefits and harms. This study will review marijuana's pharmacological effects; state of current scientific knowledge; marijuana's psychic or physiological dependence liability; public health risks; and the scope, duration and significance of abuse. This report should be available within six months and I will send the committee a copy when it is available.

The US 1998 National Drug Control Strategy notes that both law and common sense dictate that the process for approving substances as medicines be thorough and science-based. Under American procedures, laboratory and clinical data are submitted to medical experts in the Food and Drug Administration (FDA) for an evaluation of claims of the safety and efficacy of a new drug and its proposed use. If the scientific evidence is sufficient to demonstrate that the benefits of the medical use of a substance outweigh associated risks, the substance can be approved for medical use. This rigorous process protects public health. Allowing marijuana or any other drug to bypass this process is unwise.

I wish the committee much success in its important task, and will be pleased to share further information from the United States when it is available.

16 June 1998

**Memorandum by Dr David Kendall, Reader in Molecular Pharmacology,  
University of Nottingham Medical School**

1. The following evidence is submitted as a personal statement and does not necessarily reflect the views of the University of Nottingham. My background and expertise are as an experimental pharmacologist, not a clinical scientist, and my evidence is based largely on an understanding of the relevant scientific literature and interactions with clinical colleagues. For the last few years my research group has been involved with projects investigating the physiology and pharmacology of cannabinoid substances. The Medical Research Council, the Wellcome Trust and a pharmaceutical company have funded these studies. I am a qualified Pharmacist and a member of the Royal Pharmaceutical Society.

**2. Mechanism of action of cannabis**

The effects of cannabis are mainly mediated by a family of so-called *cannabinoid* substances the most important of which, certainly from the point of psychoactivity, is  $\Delta^9$ -tetrahydrocannabinol (THC). There are, however, dozens of related compounds, particularly in cannabis smoke, which might have a role in some of the effects of cannabis. This ill-defined mixture of substances ingested by cannabis users is one of the major difficulties encountered by researchers attempting to determine the biological effects of the plant material.

3. It is now well accepted that the plant cannabinoids mimic the effect of endogenous agents (*endocannabinoids*) which are produced in the brain and in other cells throughout the body. Both plant cannabinoids and the endocannabinoids are "recognised" by specialised proteins (*cannabinoid receptors*) on the surface of target cells. Occupation of these receptors sets in train a series of biochemical processes which initiate appropriate cellular responses. The endocannabinoids appear, therefore, to operate as local hormones.

4. The identification of cannabinoid receptors has made it possible to develop a series of synthetic agents which either activate the receptors (and therefore act like cannabis) or block the receptors (and, therefore, antagonise the effects of cannabis).

#### 5. *Physiological effects of cannabis*

In animals, acutely administered cannabinoids produce a characteristic series of responses:

- (a) Reduced body temperature;
- (b) Reduced locomotor function;
- (c) Analgesia;
- (d) Learning deficits and reduced short-term memory;
- (e) Increased heart rate;
- (f) Reduced intraocular pressure;
- (g) Reduced vomiting.

The magnitude of all of these effects is related to the drug dose.

6. In humans many of the same responses follow cannabinoid exposure. Not surprisingly, the subjective effects vary from person to person, the differences being due to dose and route of administration, the context in which the drug is taken, prior use and individual susceptibility to psychoactivity. In general, there is a paucity of information in the literature derived from controlled studies in which known amounts of active cannabinoid were consumed and many reports are based on anecdotal evidence. Nevertheless, there are features common to most cannabis consumers:

#### 7. *Effects on the central nervous system*

The major initial effect is a feeling of euphoria or happiness and well-being followed by sedation. Subjects' perception of time is often altered, and distortions of hearing and vision, infrequently resulting in hallucinations, are common. Unusual associations of words are frequently made. In placebo-controlled trials, smoking marijuana cigarettes has also been associated with increased anxiety, tension, anger, confusion and a significant degree of depersonalisation. The negative symptoms are most marked in naïve subjects and experienced users appear to experience a greater incidence of, and more profound, "high". Acute psychotic episodes can, infrequently, result from cannabis ingestion, but these can be classified as acute confusional states which occur in clear consciousness and the diagnosis of "cannabis psychosis" as a distinct clinical entity is unjustified. Similarly, there is no convincing evidence that cannabis has a precipitating role in either chronic psychosis or affective disorders, although the drug could modify pre-existing psychiatric disease progression. Indeed, it has recently been postulated that endocannabinoids might play a role in the aetiology of schizophrenia and cannabinoid receptor antagonists have been patented as potential anti-psychotic compounds.

8. Cannabis almost certainly impairs short term, but not long term memory and the effects, at least in adolescents, appear to persist for some weeks after abstinence from the drug. The residual impairment of short term memory (ie that which persists after a period of abstinence) is more significant in female than in male users.

9. Motor co-ordination is also impaired during cannabis intoxication leading, for instance, to problems with driving after the consumption of the equivalent of about two marijuana cigarettes. The impairment persists for four to eight hours, which is a good deal longer than the subjective effects last, and is additive to that produced by alcohol. There are, however, reports, particularly in relation to experienced users, in which driving ability is not affected, or is even improved, by a moderate intake of cannabis.

#### 10. *Effects on the immune system*

One of the cannabinoid receptors (the CB2) is highly localised to cells of the immune system and endocannabinoids are produced by those cells. It is likely, therefore, that the endocannabinoids are involved in modulation of the immune system and *in vitro* experiments indicate that cannabinoids have immunosuppressive actions. However, in clinical situations there is little evidence for such an effect at the doses of cannabis normally consumed.

#### 11. *Effects on the endocrine system*

In animal experiments, cannabinoids have been shown to influence the release of pituitary and adrenal hormones. However, in clinical studies of chronic cannabis users no effects were detected on testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin or cortisol levels in either men or women.



## 12. *Effects on the cardiovascular system*

Cannabis causes an increase in heart rate and a fall in blood pressure in humans that is partly due to an effect on sympathetic outflow from the central nervous system<sup>20</sup>. Recent animal data<sup>21</sup> support the hypothesis that endocannabinoids are important regulators of organ perfusion, acting directly on the blood vessels themselves and the plant cannabinoids might mimic this vasodilator effect. This is exemplified by the dilatation of conjunctival and scleral blood vessels which occurs in many cannabis users.

## 13. *Cannabis preparations and methods of administration.*<sup>22</sup>

THC and related cannabinoids are highly fat-soluble and after oral administration are co-absorbed with dietary lipids. Solutions of THC in sesame oil (taken as capsules) are better absorbed than solutions in ethanol. The rate of absorption can be increased by emulsifying the THC (eg using a bile salt). By far the most widely used method of administration is by smoking the crude plant material either alone or mixed with tobacco. Smoking acts to concentrate the THC and a condensate of the smoke of a marijuana cigarette contains about 16 per cent cannabinoids or five times the proportion in the unburnt marijuana. Between 15 and 50 per cent of the THC in the original plant material is absorbed by smoking. The effects of smoking cannabis are very rapid (within a few minutes) whereas orally administered preparations may take one to three hours to act. In animal experiments, only a small amount (less than 1 per cent) enters the brain due to binding to plasma proteins. THC accumulates in adipose, tissues, the lungs and liver and this prolongs its persistence in the body. Cannabis can be readily incorporated into a number of foodstuffs for oral administration (eg "cookies", spaghetti sauce) which circumvents the health hazards of smoking but can create other dangers. For instance, there have been reports of coma induced in small children who mistakenly ate cannabis cookies. It is clear that the qualitative effects of cannabis are very similar irrespective of the method of administration.

## 14. *Is cannabis addictive?*

Definitions of addiction vary from source to source and have changed over the years. Most experts now use the term "dependence" which implies that the agent in question elicits "drug seeking" behaviour, driven by a psychological craving for that drug, irrespective of social consequences. It also implies, to some people, that the drug is taken regularly in every-increasing amounts, due to the development of tolerance, and that there is an associated unpleasant withdrawal syndrome that deters abstinence. The situation with cannabis consumption is complicated by the fact that long term, heavy users of the drug inevitably abuse other substances to the same or a greater extent, making it difficult to distinguish between the drugs that are being sought.

15. Drug seeking behaviour implies that the drug is rewarding and much effort has been expended in recent years to define the neuronal reward circuits in the brain<sup>23</sup>. Some of the biochemical changes which occur in these circuits appear to be common to cannabis and the "hard" drugs of abuse (eg heroin) and this had led some researchers to conclude that cannabis is equally addictive<sup>24</sup>. The results of experiments using animal paradigms that test rewarding behaviour directly have been controversial<sup>25</sup> but, under appropriate conditions, rats and mice will self-administer cannabinoids<sup>26</sup>. Cannabinoids can also be shown to enhance the self-administration of electrical stimulation to areas of the brain associated with reward<sup>27</sup>. Humans obviously derive some satisfaction from taking cannabis, otherwise effort would not be expended to obtain it and THC has been demonstrated to have reinforcing effects in regular cannabis users<sup>28</sup>. However, the same could be said of many relatively harmless pursuits such as eating junk food or watching Everton Football Club!

16. With regard to other component features of drug dependence, there seems to be little evidence of even chronic users significantly increasing their dose of cannabis over time. This is despite the substantial evidence for the development of pharmacological tolerance to the effects of the drug. For instance, the robust hypothermic response to cannabinoids in experimental animals requires significantly greater doses to achieve the same response after only a few administrations<sup>29</sup>. Indeed, there is some evidence of "reverse tolerance" in which the amount of cannabis required to produce the same subjective effects decreases over time. This might be explained by induction of enzymes needed to manufacture psychoactive metabolites or more psychological factors such as increased familiarity with the subjective feelings, lessened anxiety associated with reduced feelings of guilt, etc.

17. The question of whether abstaining from cannabis after repeated use causes a withdrawal syndrome has been a matter of controversy. A well-defined series of symptoms can be precipitated by giving cannabinoid-treated rats a cannabinoid receptor antagonist and clinical evidence now supports the existence of an abstinence syndrome in humans, particularly in adolescents<sup>30,31</sup>. It is, however, very mild compared to that which follows withdrawal from opiates and only occurs in a minority of former habitual users. This might be related to the accumulation of cannabis in the fatty tissues leading to a gradual decline in its concentration even after abrupt withdrawal. It is, therefore, unlikely that fear of an unpleasant withdrawal response is a major factor in the abuse potential of cannabis.

## THE MEDICINAL VALUE OF CANNABIS

18. *Multiple sclerosis (MS)*

There have been many anecdotal reports of the value of herbal cannabis in alleviating the symptoms of MS. A recent study, based on a questionnaire survey of MS sufferers who had smoked cannabis, reported significant subjective improvements in a range of symptoms. There are, however, very few objective, controlled studies of cannabis use in MS and the available evidence indicates, for example, a detrimental effect of smoked cannabis on balance in patients with spastic MS<sup>33</sup>.

19. *Analgesia*

Anecdotal reports of the value of herbal cannabis in treating chronic pain resistant to other forms of analgesia abound, but to my knowledge, there have been no controlled clinical studies of the analgesic properties of cannabis in humans. However, the antinociceptive effects in laboratory animals emphasise the potential use of cannabinoids in painful conditions and the need for proper clinical evaluation. The synthetic cannabinoid levonantradol has been used in a controlled evaluation of acute, moderate to severe postoperative pain and was found to have significant benefit<sup>34</sup>. Drowsiness, in 40 per cent of patients was the only major side effect.

20. *Anti-emesis*

The use of cannabis in the control of nausea, particularly with regard to that occurring as a consequence of chemotherapy, was surveyed by the American Society of Clinical Oncology in 1994<sup>(35)</sup>. Cannabis, either as smoked marijuana or oral THC, was thought to be effective in 50 per cent of patients, although unpleasant side effects were reported by 25 per cent of treated patients. Cannabis was ranked only ninth in order of preference for the treatment of mild to moderate nausea and vomiting and sixth for more severe cases. Only 6 per cent of clinicians said that they would prescribe cannabis much more frequently if legal barriers were removed. The synthetic cannabinoid, nabilone, is marketed as an antiemetic as an adjunct to cancer chemotherapy, but it has not proved to be popular with physicians.

21. *Appetite*

Weight loss is a significant problem in AIDS patients, particularly if they are undergoing chemotherapy and marijuana has been widely used as an appetite enhancer. Again, there is no unequivocal clinical evidence to support its claimed beneficial effects although trials with dronabinol (THC) have demonstrated improved appetite at acceptable doses in AIDS patients (36). Although the clinical evidence for cannabis-induced immunosuppression in normal subjects is weak, the potential added dangers for AIDS patients cannot be ignored.

22. *Glaucoma*

Again, the anecdotal accounts of cannabis reducing raised intraocular pressure (IOP) exceed the objective evidence. THC, both topically and systemically, does not seem to lower normal intraocular pressure (37). The endogenous cannabinoid anandamide appears to reduce IOP in animals when applied topically (38), although no human studies in normotensive or glaucoma patients have been reported.

23. *Cardiovascular system*

There is increasing evidence that cannabis and its analogues dilate blood vessels directly (this is readily visible in the conjunctival vessels) and reduce blood pressure. There have been no objective clinical studies investigating the effects of cannabis on blood flow in healthy human volunteers or in hypertensive patients.

24. In conclusion, the objective evidence for positive medical effects of cannabis is relatively poor. This is hardly surprising given the dearth of clinical trials involving the drug and a relaxation of the level of control allowing such studies could be of benefit. However, it will be difficult to interpret the results of clinical studies with herbal materials consisting of poorly defined mixtures of various potentially active agents. It is much more likely that clinical benefit will be derived from the use of synthetic cannabinoids drugs in the future. The advent of such medicines would clarify the legal situation regarding the possession of herbal cannabis for medical reasons, ie there would be no argument for using herbal cannabis if quality-controlled cannabinoid medicines were available. This assumes, of course, that there is no advantage accruing from taking the mixture of different cannabinoids in the plant material and this emphasises the need for clinical studies of herbal cannabis compared with the synthetic drugs.

25. With regard to the scientific basis for maintaining the prohibition of recreational use: there is little doubt that cannabis is fundamentally a less dangerous material than other abused drugs (alcohol, tobacco, the opiates, amphetamine cocaine, ecstasy and LSD). The acute toxicity of cannabis is negligible and the



evidence for major adverse effects after chronic exposure is unconvincing. It is clear, however, that cannabis, particularly in combination with alcohol, is a contributory factor in road traffic accidents and, in its smoked form, it carries additional health risks associated with pulmonary disease. Given its wide-ranging pharmacological effect on many organ systems, it is clear that, if cannabis were a newly discovered medical product, it would be a prescription-only medicine. On this basis alone, it is hard to justify the unregulated use of cannabis as a recreational substance, but comparisons will continue to be drawn with alcohol and tobacco for which similar arguments could be made. I will be surprised if, in the future, much more potent synthetic cannabinoid drugs possibly with greater health risks, do not find their way onto the recreational market and the deregulation of herbal cannabis could make it difficult to control these agents.

30 April 1998

#### Memorandum by the London Medical Marajuana Support Group

I would like to make a submission of evidence to the Select Committee on behalf of the London Medical Marajuana Support Group. We are a coalition of medical marajuana patients and their carers. Our support group exists to provide information and assistance to those people who are under advisement from their health care practitioner that they may derive therapeutic benefit from the use of cannabis. As such we have been able to build up an increasingly comprehensive picture of the very diverse needs of a very diverse group of people. At this current time we have been providing information, advice and counselling for patients suffering from:

1. HIV/AIDS
2. Cancer
3. Multiple Sclerosis
4. Glaucoma
5. Chronic pain
6. Migraine

Obviously any change in the current legislation will directly impact us and the people we represent and we feel it is most important for us to be able to contribute to this debate with some points of view born of experience. Helping to ensure any change in the law is practical and workable for those whom it is intended to serve.

Our written submission of evidence (three pages) follows this introductory letter, along with a short scientific bibliography submitted as an appendix (available from the Clerk).

However, because we are primarily a patient based group rather than a scientific/medical research group or professional political lobbyists, we feel that we could be most effective in submitting evidence orally. I have spoken to a number of patients in the group and after some discussion two patients—one living with AIDS and the other a Chronic Pain sufferer—have been nominated and would be willing to come and speak to the committee. In addition I would be available to answer any questions about the following notes and to discuss my experience as a voluntary worker/carer.

Mark Heley

July 1998

#### *Notes on dosage and administration of medical cannabis*

##### 1. DOSAGE

1.1 As the applications of medical cannabis are extremely diverse, so are the most effective methods of preparation and administration of medical cannabis for the conditions being treated. For example, chronic pain sufferers often need to consume quite large quantities of cannabis to get a sustained analgesic effect. In addition to this, unlike “heavy” recreational users, chronic pain sufferers do not seem to quickly build tolerance and in cases of persistent and intractable pain, may medicate with quite large doses of cannabis over long periods of time, without any noticeable changes in tolerance. (This effect has also been mentioned in the testimony given to the Select Committee by Dr Montgomery of Edinburgh University).

1.2. By contrast, some Multiple Sclerosis sufferers, compared to “regular” recreational users, only need relatively small amounts of cannabis taken at quite long intervals apart to control their symptoms. This very considerable range in dosage levels means that there is no “standard” or average medical marajuana user. An effective dosage level for a particular patient with a particular set of symptoms may vary between 5g to 50g of herbal cannabis a week and needs to be set by the patient themselves, working in conjunction with their health care practitioner. This dosage level may also vary considerably over time, with chronic and acute conditions and/or palliative care requiring constant medication to help mitigate intractable symptoms and others like, Glaucoma and Migraine patients, often needing much more infrequent—or even one off—treatments to relieve symptoms.

## 2. METHODS OF PREPARATION AND ADMINISTRATION OF MEDICAL CANNABIS

### A. *Sub-lingual tincture*

Tincture of cannabis (in either alcohol or glycerin) taken sub lingually has proven to be a very effective method of administration of medical cannabis for many patients. The effects are relatively immediate, yet dosage can be controlled more exactly than with cannabis foods and drinks. Any potential carcinogenic risk from inhaling smoke is avoided by this method of administration. Tinctures can be made that cover the whole range of psychoactive effects by selecting appropriate strains of the plant from which to make the tincture. For example, tinctures made from “lighter” strains of cannabis, such as Thai or Purple Haze, are particularly suitable for more psychoactive complaints such as Migraine. Homeopathic tinctures have also proven effective and can be made by progressive dilution for those who are particularly sensitive to the effects of cannabis, or who are children.

### B. *Food and drink*

Cannabis can be made into a drink by heating it in any fat containing liquid, like soya or dairy milk. Heating either 10g–15g of cannabis leaves or flowers or both to a slow boil and then simmering it for 15 minutes in one litre of milk is sufficient to create the drink known in India as a *Bhang Lassi*, which has proven to be an excellent analgesic for sufferers of chronic pain, to stimulate appetite in people living with HIV/AIDS, to relieve nausea and other side effects associated with chemotherapy. Bhang Lassi is more dosage flexible than eating cannabis or cannabis derivatives, which is usually done by baking them into cakes or flapjacks.

Cannabis food, including cannabis porridges and gruels for those who find it difficult to eat, is very effective in extreme cases such as palliative care for the terminally ill or to provide for the relief of chronic constipation associated with opiate usage in palliative care. Cannabis food is particularly suitable to the administration of higher dosages of cannabis and as such is only particularly appropriate for those conditions which require persistent, on-going medication over three to five hour periods at a time.

It has also been noticed that there is a synergistic effect between psychoactive cannabis food and eating non-psychoactive cannabis seeds. The “hemp seed” providing in its oil, which is very high in GLA, LNA and other linoleic acids, precursors to the neurotransmitters which are activated by the psychoactive elements of cannabis. This can make the experience more stable, balanced and “organic” for the patient and has been adopted by many medical marijuana patients.

### C. *Vaporiser*

The most safe way yet derived of inhaling cannabis is through a device called a vaporiser. Basically consisting of a heating element placed inside a jar, from which vapour is drawn through a piece of plastic tubing. The heating element heats the plant material to the exact point of THC vaporisation, so that only pure THC vapour is inhaled, with little or none of the heavier cannabinoids or tars that have been associated with the health risks in smoking. This device has proven to be very effective for treating wasting syndrome in people living with HIV/AIDS and appetite loss associated with cancer and the effects of chemotherapy.

### D. *Smoking*

Smoking is still the preferred method of administration for many of those medical marijuana patients who were previously recreational users. Health risks associated with smoking can be reduced by the use of water pipes to cool the smoke, smoking herbal cannabis rather than resin and especially not mixing cannabis with tobacco, which has proven serious health risks.

Smoking is the most easy way to administer a flexible dosage of cannabis so that the experience does not become uncomfortable for the user and is preferred often by those using the lightest dosages of medical marijuana. For medical marijuana patients who have not been recreational users, there is often a social stigma attached to smoking and in cases where medical marijuana users have preferred not to smoke, alternate methods of administration have been found for them, so there has been no necessity for them to do so.

## 3. DIFFERENT STRAINS OF CANNABIS HAVE DIFFERENT MEDICAL EFFECTS

3.1 It is not only the THC in cannabis which has a psychoactive effect, the presence of many of the other cannabinoids, especially CBN and CBD in varying different proportions, determines the length and character of the psychoactive effects. The more CBN and CBD, the greater the intensity of body related sensations, the less CBN and CBD and the THC, the more mentally active the stimulation will generally be. High CBN and CBD cannabis is more effective for the control of symptoms which are felt as being body related, such as chronic pain. High THC cannabis has been most effective in treating, for example, people living with HIV/AIDS, who don't usually desire the “heavily stoned” feeling and/or the lethargy that High CBN/CBD cannabis can create.



#### 4. HERBAL CANNABIS VS CANNABIS-DERIVED PHARMACEUTICALS

4.1 The vast majority of medical marajuana patients, given the choice between cannabis-derived pharmaceuticals like Nabilone and Marinol and herbal cannabis, will prefer herbal cannabis. This is for several reasons.

A. Administration of dosage is much more flexible with herbal cannabis than with pharmaceuticals.

B. Different kinds of cannabis are more or less suited to different medical conditions (For example, Dr Montgomery of the University of Edinburgh cited in his testimony to the committee differences between Nepalese Black suitability for analgesia and Thai Grass for Migraine). The medical marajuana patient who is also able to grow their own plants is hence put at a considerable advantage to those who are unable or unwilling to do so, because they are able, by the process of ongoing selection of plants, to cultivate strains that are particularly well suited to their own individual medical conditions.

C. Cannabis derived pharmaceuticals have more side effects than herbal cannabis. More frequent unpleasant overdose experiences are reported than with herbal cannabis and although some patients respond to pharmaceuticals, not all do—and some medical marajuana patients who are able to self medicate satisfactorily using herbal cannabis report no benefits at all from taking cannabis derived pharmaceuticals.

4.2 We strongly feel the problems associated with cannabis based pharmaceuticals can be avoided by making herbal cannabis available to those people who are currently prescribed these drugs. By changing the legislation to allow medical marajuana patients to either grow their own medical cannabis, creating medical cannabis growing co-operatives for those unable to grow, or allowing the commercial cultivation of medical herbal cannabis, on the grounds of compassionate usage. This would allow the diverse range of medical marajuana users to access the appropriate medication for their condition: the right strain of cannabis and the necessary information from a health care practitioner on dosage and the right method of administration. In view of this inherent diversity of the different strains of cannabis and their differing suitability for different medical applications we also feel that it will not be sufficient merely to change the scheduling of cannabis to allow doctors to prescribe a standardised herbal preparation or extract of cannabis, although such a change in the law would be a considerable improvement over the current situation.

#### 5. WHAT IS MEDICAL GRADE CANNABIS?

5.1 The London Medical Marajuana Support Group works with several herbalists based in and around London. The consensus amongst these qualified professionals is that herbal cannabis can only really be considered to be of medical grade when it is grown organically and in soil. Because of the nature of the plant—and the literally billionfold permutations that are possible of the 60 or more cannabinoids—the medical qualities of the plant will always be changing as the particular cannabinoid profile evolves through the process of natural gene selection. Although this precludes creating a standardised extract of cannabis that is effective for the whole of the diverse range of patients being treated with medical marajuana, it does not preclude creating medical grade herbal cannabis and its extracts that are standardised—in the terms and conditions under which they are grown, prepared and harvested—in the same way that is demanded of other medical herbs and herbal medicines.

#### 6. A MEDICAL CANNABIS PATIENT REGISTRATION SCHEME

6.1 As an alternative, or as an addition to this change in the law, we would like to propose a medical cannabis patient registration scheme granting licenses to possess or grow appropriate amounts of medical herbal cannabis on a named patient basis. This, we feel, should be sufficient both to clearly separate medical users of cannabis from recreational users and to ensure that the chronically ill get access to the most appropriate medication.

*Postscript: Medical marajuana—an issue of patient's rights*  
(A statement on behalf of the London Medical Marijuana Support Group)

“We strongly feel that at the core of the many issues surrounding medical marajuana, too often the issue of patients' rights is underemphasised. The right of the terminally or chronically ill to have access to medicines that may ease their suffering and relieve symptoms that have proved otherwise intractable by other treatments. When clearly—in these cases—the relative risk posed to these patients' health by ingesting the appropriate amount of medical grade herbal cannabis by an appropriate method of administration is negligible and far outweighed by its many beneficial properties. The current legislation unduly punishes sick and dying people at the expense of a political enforcement of the laws relating to recreational marajuana usage. The appropriate place for medical marajuana is the institutions of healthcare, not street corner deals. Please do not continue to make sick people criminals.”

Thank you for allowing us to submit this evidence, especially as we were unable to meet your formal deadline. We would be happy to answer any questions and provide further information about any of the material enclosed in this submission.

### Memorandum by the Medicines Control Agency

I am responding to your request dated 29 June 1998 on behalf of the above Sub-Committee to provide a note describing briefly how the MCA goes about licensing and regulating herbal medicines including an explanation of the status of the many "herbal remedies."

Please find attached a brief outline of the regulation of herbal medicine by the MCA. If Lord Perry or any member of his committee would like any further information please do not hesitate to contact me.

Dr Brian Davis  
Clinical Trials Manager

14 July 1998

## REGULATORY ASPECTS OF HERBAL MEDICINE

### What is a medicinal product?

#### 1. Under EEC Directive 65/65 a medicinal product is defined as

- any substance or combination of substances presented for treating or preventing disease in human beings or animals;
- any substance or combination of substances which may be administered to human beings or animals with a view to making a diagnosis or to restoring, correcting or modifying physiological functions in human beings or animals is likewise considered a medicinal product.

2. In summary, a product is a medicine if it is either medicinal by *presentation* or medicinal by *function*. Some herbal products do not fall within these definitions and are therefore subject to other requirements as appropriate (eg food law). The remainder of this note, however, assumes that the herbal product is classified by the Medicines Control Agency (MCA) as a medicine.

### Requirement for marketing authorisation (licensing)

3. In the UK, medicines legislation requires all medicines to be authorised (licensed) before being placed on the market, unless exempted from that requirement. Products sold or supplied for human use as medicinal products are controlled under the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994 SI 3144 and the Medicines Act 1968 and are regulated by the MCA as the Licensing Authority.

4. Herbal medicinal products sold with therapeutic claims are subject to the requirement for a product licence (marketing authorisation) and manufacturers are subject to inspection and compliance with Good Manufacturing Practice (GMP). Currently, herbal medicinal products are assessed in line with European legislation. Applications for herbal products are handled in the same way as other medicinal products. Where an applicant seeks to licence a herbal product where the ingredient(s) is not currently licensed, the product would fall within the "new active substance" category and a full dossier would be required.

5. Where the herbal ingredients are already used in licensed products, applications can be submitted under the abridged procedure. If the proposed indications are already approved for a given herbal ingredient the applicant will normally refer to published data to support the safety and efficacy aspects of the application. If an applicant proposes a new indication, a new route of administration or a new patient population, the application will be considered as a "complex" abridged application and appropriate clinical and toxicological data will be required to support the proposed use. In all cases a full pharmaceutical dossier is required relating to the formulation proposed for marketing.

6. The majority of licensed herbal medicinal products available in the UK, of which there are approximately 500, have been on the market for some considerable time. Most products originally held Product Licences of Right (PLRs) and these were granted automatically to products already on the market when the Medicines Act came into force in the early 1970's. All PLRs were reviewed by 1990 in accordance with European Directives.

7. During the review of herbal remedies, the Licensing Authority on the advice of its Advisory Bodies agreed to accept bibliographic evidence of safety and efficacy provided the product was intended for minor self-limiting conditions. No evidence was required from new clinical trials provided the manufacturer labelled the product as a "traditional herbal remedy for the symptomatic relief of . . ." and included "if symptoms persist consult your doctor". The Licensing Authority was not, however, prepared to relax the requirements for proof of efficacy for products indicated for more serious indications eg hypertension.



### Exemptions from licensing requirements

8. Section 12 of the Medicines Act 1968 allows exemption from product and manufacturers' licence requirements for herbal remedies sold or supplied in very specific circumstances. The exempt products are those supplied by herbalists to individual patients on the recommendation of the practitioner. Also exempt are products consisting of dried, crushed or comminuted herbs (ie those made from simple processes). In both cases the exempt products are supplied without written recommendations as to their use.

### Retail sale and supply

9. The sale of potentially hazardous herbal products has been restricted in two ways. Certain plants such as *Digitalis*, *Rauwolfia* and *Strychnos* are not permitted under the herbal exemptions and are specifically controlled under the Medicines Act as Prescription Only Medicines (POM). (However, as long as the product concerned is a herbal remedy made from simple processes a shopkeeper (ie not necessarily a pharmacist) may sell or supply against the prescription of an approved practitioner (generally a doctor), unless the POM Order specifies to the contrary.) In addition, other herbal ingredients are controlled under The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977 SI 2130. This Order specifies plants which cannot be supplied except through pharmacies and also restricts the doses and route of administration of other herbal ingredients used by herbalists.

### EU initiatives

10. Herbal medicinal products are available in all Member States within the European Union and there are important initiatives underway within the Community to harmonise the way these products are regulated. This is to ensure that herbal medicinal products have unhindered access to the single market. To progress this initiative the European Commission has established an Ad Hoc Working Group on Herbal Medicinal Products to review the criteria for marketing authorisations. The Commission have also commissioned a major study of the regulatory control of herbal products within individual member states and this study is currently being undertaken by the Association Européenne Pharmaceutiques Grand Public (AESGP).

### Conclusion

11. This note is not intended as a comprehensive statement of the relevant regulatory requirements. For example, there are other detailed requirements and restrictions relating to labelling and advertising.

12. In summary, the law relating to the herbal exemptions from licensing requirements and to the retail sale and supply of herbal remedies (both licensed and unlicensed) is rather complex. There are several mechanisms which can be considered where there are concerns about the need to control the sale and supply of a specific herbal remedy.

### Memorandum by Tod H Mikuriya, MD, Medical Co-ordinator, California Cannabis Centers

My good friend Matthew Atha, contributor to the Indian Hemp Drugs Commission Centennial Volume, 1994 suggested I contact you to offer my testimony concerning my clinical research into the medicinal uses of the drug.

I have performed some seven hundred structured medical interviews in California cannabis centers regarding reasons for self medication with cannabis. They have both reaffirmed medicinal uses described before removal from prescriptive availability in 1937 and added many more.

One of the most dramatic findings is the comparative safety of cannabis utilised medicinally with accepted pharmaceutical interventions. The efficacy without adverse side effect difference was so great as to risk involvement in criminal activity.

Cannabis is effective in the management of chronic conditions involving inflammation, spasticity, and pain. Its analgesic effects are from local anti inflammatory plus altered perception at the higher centers of the brain.

Cannabis an immunomodulator.

With a low intake at levels sometime less than 5 grams a week of quality smoked cannabis. The use of cannabis is worked into other parts of the individual's coping regimen. It is my speculation that alterations in cerebral functioning cause salutary effects on neurohumoral behaviour of the pituitary adrenal axis.

Cannabis is a mood modulator with potent antimania and antidepressant properties. Again, the freedom from unwanted side affects compared with other psychotropics, is a salient reason for self medication with cannabis. As an anticonvulsant, do ask MI-5 what they know from their researches in the 50s through the 70s—and who knows?

The mechanisms of action appear to be both neural and psychological. There is increased cerebral circulation, decreased anxiety, decreased emotional reactivity, and decreased insomnia. Decreased short term memory relieves obsessive thinking. Altered time space perception decreases reaction to pain.

While cannabis was generally used in oral form, the dose was more reliable and inexpensive. The expense and variability of the illicit drug precludes return to this preprohibition preferred route. The use of vaporisation inhalation methods avoids the undesired irritation of the tracheobronchial tissues. In California we are trying out these technics in some cannabis centers.

This clinical research I have performed personally is in a population officially defined as similar to the "dissolute and depraved" visited by Sir W.B. O'Shaughnessy in 1838 in Bengal.

Cannabis prohibition is a lingering offshoot of the American disease of alcohol Prohibition that was repealed in 1933. Harry J. Anslinger, head of the Federal Bureau of Narcotics mounted a job saving reefer madness campaign and added cannabis to its purview. International bullying by the U.S. ensured spread of the disease.

Censorship and intimidation have had their corrosive effects on the clinical body of medical knowledge thus harming patients from exposure to more dangerous. Wrong headed public policy that involves police in a medical problem for which they lack expertise plus their mere contact is harmful. Worse, and more fundamental, cannabis prohibition causes injury to the self esteem of the cannabis medicator who is otherwise a good citizen and responsible member of the community.

I would be more than pleased to present my work to your respected body.

### **Memorandum by the National Drug Prevention Alliance**

CANNABIS: ARGUMENTS AS TO MEDICAL AND/OR RECREATIONAL USE. OR NOT.

#### *1. Background*

1.1 This submission by NDPA responds to the terms within the Committee's Call for Evidence, dated 4 March 1998.

1.2 NDPA is a non-sectarian, non-party-political grouping of professional and lay bodies interested in the advancement of healthy, drug-abuse-free lifestyles. NDPA has been an invited participant in other senior policy processes. Regular contacts exist with the office of the UK Anti-Drug Co-ordinator, CDCU, Home Office, DfEE, DoH, Police forces, DATs, DRGs and such prominent authorities as Professor John Henry and Professor Heather Ashton, NDPA's international network is particularly strong.

1.3 NDPA and its constituents have sustained a special study of all aspects of cannabis for more than 10 years, and have (within resource limits) explored and studied the international research.

#### *2. Terms of Reference and Terminology*

We are pleased to see the avoidance of the obfuscatory term "Legalise for Medicine"—a redundancy in terms which does much to confuse the public, which is doubtless the intention.

The Committee's specific focus is noted, but NDPA wish to place on record their disquiet in five particular respects, which are:

- 2.1 exclusion of some kinds of scientific evidence;
- 2.2 reliance on a small, private committee for other evidence;
- 2.3 use of "leading" terminology and phrasing in the Call for Evidence;
- 2.4 no recognition of Total Health; and
- 2.5 three neglected areas in public consciousness.

Our concern is that these and other factors may jeopardise the proper execution of the brief; expanding slightly on these headings, by way of explanation:

##### *2.1 Exclusion of certain kinds of scientific evidence*

Most, if not all, the headings (factors) listed at the foot of page 1 of the Call for Evidence, and which the Committee will not consider, are the subject of scientific observation/analysis. In terms of impact on society as a whole it can be argued that such factors may be of greater significance than the (medically oriented) "physical or psychological effects". We cannot therefore see how the Committee can reach a meaningful verdict on "How strong is the scientific evidence in" without taking full account of all relevant scientific factors.

##### *2.2 Reliance on small, private committee*

The Police Foundation has announced its intention to review certain factors around (*inter alia*) cannabis, as part of a reassessment of the 1971 Misuse of Drugs Act. We are advised that the Police Foundation has no formal association with the police, has no statutory standing, and has a self-appointed group of 13 people



conducting this assessment *in vacuo*. We already have concerns about several of these 13, either for their extant expressions in national newspapers or elsewhere in favour of law relaxation (or law deletion) or for their association with the bodies known to take a particular stance on drug policy. Whilst they have a position antipathetic to our own, this is of less overall significance than that the Police Foundation review body is far from being neutral on the subject. We are in contact with them (as invited commentators) and we shall do our best to pursue the exercise with them constructively, but we remain deeply concerned that the Lords Select Committee would imply reliance on any such narrowly-based and possibly partisan body—whether such body supports us or not.

### 2.3 Leading terminology and phrasing

We are concerned that certain “trigger words” known to have been insinuated into general public/media use by the pro-drug movement are used here.

“Prohibition” is one such; our current British drug laws have nothing to do with a failed American attempt to stop a socially-accepted drug being consumed; they instead relate to generally socially-rejected drugs being released from existing constraints on non-medical use, which ever surveys by pro-drug entities such as *The Independent on Sunday* show two-thirds of the population against law relaxation. The correct term, we respectfully suggest, is illegality.

“Recreational Use” generates a false construct. There is nothing re-creative about the ingestion of substances to intoxicating levels. The correct term, we respectfully suggest, is either “Non-Medical Use” or “Abuse”.

When it comes to our concern about leading questions we have in mind that your phrases tend to be couched in one direction, ie towards approval; for example:

“What evidence . . . has valuable medicinal actions?”

“promoting clinical trials even if current level of control is maintained?”

“... evidence in favour . . . medical use?”

“... evidence in favour . . . prohibition of recreational use?”

Of course one can construct a defence for this phrasing, but we need to have the Committee recognise our concern on this. After all, there have been other ostensibly scientific studies of cannabis in the past where it transpired subsequently that a particular agenda was influencing proceedings.

### 2.4 Total Health

We are sure the Committee will wish to recognise that such as WHO, and many agencies long before them, have identified the wide-ranging nature of Total Health. Typical listings of constituent parts include:

- Physical (physiological)
- Mental (psychological, psychiatric)
- Intellectual (potential of the brain)
- Emotional
- Social
- Spiritual
- Environmental

### 2.5 Areas of Neglect in Public Consciousness

(a) It is NDPA’s experience, and that of its partners in at least some other countries, that three areas of concern about drug abuse in general, and cannabis abuse in particular, are largely neglected. These are:

- full extent of health consequences;
- full extent of harms; and
- extent of population harmed.

(b) The tendency is for public consciousness to be focused solely on the user, on the extremes of harm he/she eventually experiences, and for harm only to be considered in physiological terms. This is an appalling (and for some at least, tendentious) compression of the true situation.

(c) Taking each of these neglected areas in turn, we would suggest that a full assessment of health consequences should address each of the headings in our definition of “Total Health” in Section 2.4 above. Total harm to society’s health will in part derive from the prevalence of use, therefore a greater number of less intensive users may cost society more than a smaller number of drug dependents (*The Sunday Times* commissioned research on alcohol around 10 years ago which concluded in this vein). Moreover, greater prevalence generally predicts greater harm to society overall. From this basis it is reasonable to conclude that,

in Britain, cannabis use may cost society more than heroin use; research to put numbers to this hypothesis would be very valuable.

(d) Other related considerations are the variation in harm with degree of involvement, and the consequences for people other than the user. Whilst everyone can identify with the major harm to self caused by a drug dependant (an “addict”), fewer will readily recognise the harm to others deriving from the first discovery of use; use which may only be at the first, tentative stages. Stress is now widely recognised as a psychological condition capable of prompting physiological harms. It follows that, on the micro scale, significant others close to the user will experience stresses of varying degrees which depending on their extant condition, may provoke more profound consequences. This will generally be exacerbated as the user’s degree of involvement increases. Clearly, too, physical harm may accrue to others through the intoxication (the “high”) of users who access machinery, equipment or vehicles while in this state, and physical harm often carries with it a psychological penalty.

(e) The sum total of these three areas of wider harm when taken on the macro scale, and in association with what is already more generally understood as to physiological and psychological harms, adds up to a conclusive argument against the non-medical use—and in certain respects the medical use—of this dangerous substance.

### 3. *What are the Physiological Effects (Immediate, Long-Term and Cumulative) of Taking Cannabis in its Various Forms?*

3.1 In the interests of brevity we would mention here that we have shared research information with others such as Professor John Henry, Professor Heather Ashton, the Christian Institute (Newcastle-upon-Tyne), Mrs Mary Brett of Amersham, in Buckinghamshire, Dr Janet Lapey of Hanover in Massachusetts, Professor Gabriel Nahas of New York, and Dr Harold Voth and Dr Richard Schwarz of the International Drug Strategy Institute. Some or all of these may present evidence to you. We will do our best not to overlap with them.

3.2 One of the prime sources of research papers is the Mississippi University Department of Pharmacology. Mississippi has long had an active engagement with the subject, and under the leadership of such as Dr Carlton Turner (who went on to become the then President’s Drug Advisor, or “Tsar”) has been licensed to grow cannabis for experimental purposes. More than 12,000 scientific papers have been collected to date—the great weight of these testify to the significant harms (physiological, psychological and other) from the abuse of cannabis and few, if any, give cannabis “a clean bill of health”.

3.3 For the record, our feeling is that if a hypothetical substance were to have just two research studies about it—one positive and one negative—prudence demands that the negative result controls and we must err on the side of caution.

3.4 Several exemplary collations/overviews of medical scientific research exist. Among these we would recommend:

Paris Symposiums 1990 and 1992 (Ref)

Marijuana in the Decade of the Brain (Ref)

Proceedings of the Houston Conference (Gabriel Nahas et al) 1998

Marijuana: Myths & Misconceptions (video) Robert Gilkeson MD, Venice, CA

POST Report

*Marijuana—Deceptive Weed*, Gabriel Nahas, MD.

3.5 Drawing out some principal findings from these and other such collations, we conclude that:

- Cannabis use is significantly physiologically harmful in the mid to long term whatever its strength;
- Higher strength grades may prove physiologically harmful even in the short term; and
- Harm may occur in terms of cancers, immune system damage, brain cell impairment, accumulation of cannabis molecules in vital organs, foetal damage, addiction, and motor skills impairment.

The sum total of research papers at Mississippi University may seem large but is, we understand, small in comparison with the body of papers relating to eg tobacco; reportedly over half a million. If and when the body of papers for cannabis approaches this figure, it seems likely from the above that even more harms will have been identified.

### 4. *What are the psychological effects?*

4.1 In general the remarks made in Sections 2.4 and 2.5 apply similarly to psychological aspects. Many of the WHO elements of Total Health have a psychological component. The effects on other people’s psychological health, and the progression with increasing use, starting not with addiction but with first use are all valid parts of the total picture.



4.2 The ability of certain drugs to trigger otherwise latent psychoses was (arguably) first noted in relation to abuse of LSD. More recently experts such as Prof John Henry have described the capability of especially the stronger grades of cannabis ("skunk", "nederweed" etc with THC contents up to 30 per cent or more—compared to 0.5 per cent with "Mexican Grass" such as was on the street in the 1960s) to trigger psychosis. As one apologia for cannabis abuse some of its advocates manipulate this information to suggest that only the "feeble-minded, or the ill-in-waiting" are at risk, unlike the regular chap. No evidence is offered to support what seems to be a very dangerous and opportunistic reconstruction of the facts.

4.3 The variation of effect with age of user must be an area of considerable concern to the Committee. Age of onset is dropping significantly, year on year, and children as young as seven or eight are now being anecdotally reported as users. It is already known (mainly from alcohol research) that dependency can set in much faster with young users.

4.4 Negative psychological outcomes from use when young or—in the extreme—"inherited" from parental use will be another area of concern to the Committee.

Some area of concern which are worth of further study include:

- (a) correlation with violence;
- (b) correlation with suicide;
- (c) correlation with negative classroom behaviour; and
- (d) correlation with delinquency.

4.5 Dr Janet Lapey of Hanover, Massachusetts is known to be researching (a) now, and (b) can be viewed as a form of "violence on self or a consequence of repression, therefore some interrelation may become apparent. As to (c) it has been known for some time that parental use of cannabis can cause low birth weight, reduced head diameter, hyperactivity, irrational anger and frustration, ADDS, rapid gratification drive, and disruptive behaviour. All these are typical of classroom disrupters, a syndrome which is observed to be escalating in primary schools, but which as yet is not—within our knowledge—being researched for causal links with parental use of cannabis. (The book *Marijuana Babies* discusses problems at schools for children born to cannabis using parents).

## 5. To what extent is cannabis addictive?

5.1 It is the (anecdotal) experience of drug agency workers (including this writer) who work face-to-face with cannabis users that dependency on (addiction to) cannabis can develop in both the physical and the psychological respects. The question as posed by the Committee accepts addictiveness *per se*.

5.2 Relativism between physical and psychological dependency is a cornerstone of cannabis apologists; they repeatedly assert that cannabis "isn't addictive" or is "not a problem" because "you only come to depend on it psychologically". (Ref ISDD etc). Even were this to be so (and the evidence shows that it is not) the experience of drug workers is that psychological dependency is much more intractable than physical dependency. Using the better known example of heroin addiction, withdrawal and associated physical symptoms can be completed within six weeks (and rapid detox systems are now being offered), but psychological dependency can take months or even years to remove.

5.3 The parallels between heroin cessation and cannabis cessation are significant, but an extra dimension is the extent to which a particular user has an affinity for a particular substance. Within the drug agency experience of this writer, clients have been observed who quit their physical and psychological dependency on heroin within months, but took over two years to shrug off their dependency on cannabis.

## 6. To what extent do users develop tolerance to cannabis?

6.1 Increased use with time is the rule rather than the exception, in the experience of drug agency workers (including this writer).

## 7. Postulated Medical Benefit, or not

7.1 In assessing the integrity of postulations for medical use one has two options: either (a) treat the argument and evidence *in vacuo*, on its own scientific merits or (b) review the arguments and evidence within the environment in which it was generated. It is our contention that certain of the evidence-gathering has been skewed by the environment from which it came and this has resulted in a significant imbalance in the evidence. The cannabis barrel has been scraped with such intensity and preoccupation that other, perhaps better barrels have been largely ignored. Moreover, the intense media coverage of this subject coupled with emotive highlighting of the needs of the sick cannot fail to have impacted on the members of the Committee. The environment must therefore, we respectfully submit, be taken into account when weighing the evidence.

7.2 The Committee will be aware of examples of what we mean in 7.1 above. In an attempt to encapsulate the situation we offer below a suggestion of the main milestones to date:

Years BC—Use of cannabis as herbal remedy in various cultures, in various preparations.

- 1932—Cannabis deleted from British medical pharmacopoeia because of unreliability, impurity, uneven mix of results.
- 1960s—Cannabis abuse prevalence accelerates in America due to sub-culture developments, non-violent protest mechanisms etc.
- 1971—Misuse of Drugs Act regulates the British situation.
- Early 1970s—NORML (National Organisation for Reform of Marijuana Laws) states publicly that:  
 “We will use the medical marijuana argument as a red herring, to give pot a good name”  
 (Conference, Emory University, Georgia, USA)  
 Robert Randall (and a few others) given dispensation to use smokeable cannabis in attempt to mitigate glaucoma,  
 Randall’s (and most others) dispensation revoked because of no benefits.
- 1989—DEA denies re-scheduling of marijuana.
- 1990s—NORML again publicly announce:  
 “Once we have . . . thousands . . . of people using marijuana for medicine . . . the whole scam is going to be bought. Marijuana is our strongest suit. It is our point of leverage which will move us toward the legislation of marijuana for personal use”. (Richie Cowans)
- 1997—Sunday Independent propaganda war.

## 8. Which Diseases?

8.1 Diseases or conditions for which medical benefit from “raw” cannabis use are claimed include MS, glaucoma, pain, nausea and vomiting. Others within the NDPA network will be commenting in detail on this; in summary, where reputable overviews of the research have been conducted (see Nahas. Section 4) these find against the use of raw cannabis by any ingestion method, and particularly reject the notion of a smokeable medicine. Overviews to date include:

- 1989—US DEA Rescheduling petition denied  
 1994—US Assistant Secretary of Health  
 1997—Dr Eric Voth, Dr Richard Schwartz  
 1997—BMA “The Medical Uses of Cannabis”

8.2 As a generalisation, the pro-cannabis lobby rely on motley anecdote and argument; this is contested and—in our opinion—dismissed by clinical analysis supported by relevant anecdotes and observations.

8.3 One disturbing aspect of the scientific medical scene has been the extent to which ostensibly professional institutions become “hi-jacked” by special pleading. This has happened in Britain to the BMA, via *The Lancet*, and *The BMJ* and in America to the AMA, via articles in the prestigious *NEJM*. Both *The Lancet* and *The BMJ* have published editorials eulogising medical application of cannabis; these editorials came under criticism from members but nothing was done to rescind them. Both pieces are opinion by people concerned with the production of the magazine, they do not represent any considered view by the membership of the BMA and—as can now be seen with the publication of the BMA’s report “The Therapeutic Uses of Cannabis”—they are at odds with the BMA’s position. The excellent scientific report by Professor Ashton is almost totally negated by being sandwiched between unscientific anecdotes. Even the title is misleading—since the conclusions of the report show little therapeutic uses of cannabis and only suggest more research into the possible therapeutic uses of extracts of cannabis. Yet these articles are constantly put forward as authoritative statements, by implication emanating from “doctors”.

8.4 In contrast, American doctors acted much more strongly in taking exception to the editorial by Jerome Kassirer in the *New England Journal of Medicine* (30 Jan, 1997). Four professors of medicine (Nahas et al) had a letter published in the *Wall Street Journal* (11 Mar, 1997) and elsewhere refuting the assertions of Kassirer, this led to a statement by the Board of the *NEMJ* dissociating itself from its own Editor’s comments.

Recently the media declared that the WHO report had declared “cannabis to be less harmful than tobacco or alcohol” and also stated that parts of their report had been “suppressed”. This was later corrected by the WHO—but damage had been done and many more members of the general public were led to believe that cannabis is totally harmless.

8.5 The AMA was itself an unwitting vehicle for a “medical marijuana” scam in the early 1990s when Kleiman and Doblin perpetrated a survey and analysis of doctors’ opinions. The findings as published purported to demonstrate a majority support amongst doctors, for medical use. On closer examination the survey was found to contain leading questions and its analysis to contain several questionable procedures; the numbers of doctors responding to the survey was later shown to be very small and the percentage wanting marijuana used for therapeutic purposes was only about 2 per cent of those responding. The survey was discredited, but not before it had been published coast-to-coast. These questionable surveys and reports are constantly being referred to—and are taken by the general public to be “evidence” that “doctors” believe marijuana should “be legalised”.



8.6 The committee has posed the question of whether clinical trials should be promoted even if the current level of control is maintained. Our position on this is that any scientifically-based, properly-conducted exploration of any potential medicine is appropriate, provided always that the usual protocols for testing safety, effectiveness and reliability are honoured; and that any subsequent use is limited to availability on prescription by doctors.

8.7 We would ask the Committee to bear in mind two additional points when judging on this aspect:

- there has been a disproportionate emphasis for over 25 years on the choice of cannabis as a potential medicine, which has undoubtedly stemmed from heavy promotion by the so-called “recreational use” lobby. (This has accelerated with major funding input to the lobby groups from such as George Soros, Richard Dennis etc—publicly acknowledged to be well in excess of \$20 million.) We would urge the Committee to recommend a return to balance and perspective in the exploration of nil potential medicines for these conditions, setting aside this compulsive concentration on cannabis as the elixir. It is not unreasonable to suppose, from what is known of drug abuse and addiction levels within the medical profession (BMA figures show 14,000 addicted doctors) that special pleading may be taking place.
- more recently pressure for specific diseases (most notably Alliance for Cannabis Therapeutics—ACT, originally formed in the USA and now with a British branch) have merged with the recreational use lobbies, as some of their members have had their attention drawn to cannabis, have tried it, and have perceived some benefit (almost always relating to smoking the substance and sometimes explained by the feelings of euphoria more than clinically observed results).

8.8 We are concerned to note that ACT in America is a very close “fellow-traveler” of the “recreational use” lobbies, and it is not always clear who is leading whom. ACT in this country frequently appear alongside the “recreational use” lobbyists and can be seen (in the “Green Room” etc) to be very familiar with each other.

8.9 We are even more concerned to note that in the “topping and tailing” of Professor Ashton’s otherwise commendable report, other members of the BMA have seen fit to propose that normal test protocols should be by-passed in the case of cannabis. We can see no justification in science, or indeed in the interests of patients for such an extraordinary aberration and we urge the Committee to reject it. Even when procedures are complete, negative outcomes still occur; benzodiazepines and thalidomide are but two examples. Short cuts are not the answer and would never be considered for any other drug; the interests of public safety and individuals’ total health should come before the demands of the “legalisation for recreational use” lobby.

8.10 We have heard it said by some authorities that pharmaceutical companies are likely to prove reluctant to embark on clinical trials for further cannabis (or cannabis derivatives) medicines, simply because the size of the potential market is too small to merit the research/test expenditure. Even if this were so, this would not be grounds for expedient shortcutting of the approved protocols. It might however, be grounds for grand aiding the clinical trials provided that pre-commissioning analysis (with which—as we understand it—DoH and others are familiar) demonstrated that in relation to other extant or potential medicines cannabis or cannabis derivatives had something to offer.

## 9. *How strong is the evidence?*

9.1 Clearly this is for the Committee (on this occasion) to produce a position upon, but we would respectfully submit it that there is no case to answer for either extension of medical use beyond that that already sanctioned, or for so-called “recreational” use.

The two are largely symbiotic, and if separated would almost certainly expire—and rightly so. Other very detailed inquiries have already reported and are unanimous in their conclusions—we have no doubt that the Lords Committee will find incontrovertible evidence that cannabis is not the “harmless” or “medically useful” substance that some would have us believe.

*Peter Stoker*  
National Director

20 April 1998

## Memorandum by the NHS National Teratology Information Service

At the request of Sarah-Jane Stagg of the British Pharmacological Society I am sending you our data on cannabis exposure in pregnancy (*not printed*).

The UK National Teratology Information Service is funded by the Department of Health, and actively monitors and disseminates information to health professionals on specific hazards of drug and chemical exposures in pregnancy. It also supports the National Poisons Information Service and collaborates with the HSE to monitor environmental and occupational chemical exposures.

During the last three years the number of enquiries concerning exposure to drugs of abuse has greatly increased. Since few data exist on the potential fetotoxicity of some of the newer drugs of abuse we

prospectively follow up these enquiries to determine the outcome of pregnancy. I have pleasure in enclosing our summary on the effects of cannabis in pregnancy.

We would not recommend the legalisation of cannabis because of the potential fetotoxicity that may occur if it is used during pregnancy. It is not clear from the limited data that exists whether cannabis might act as a behavioural teratogen, adversely affecting postnatal development.

*Dr Patricia McElhatton*

Teratologist, Honorary Lecturer in Reproductive Toxicology

11 May 1998

#### **Memorandum by David Nutt, Professor of Psychopharmacology, University of Bristol**

I am David J Nutt, Professor of Psychopharmacology, Head of the Department of Clinical Medicine. I am a practising Clinical Psychiatrist who runs a large research group, a broad section of which is in drug abuse.

Issues relating to cannabis for the Lords to consider:

1. There is a myth being perpetuated that the therapeutic benefits of cannabinoids are being denied patients. This is false: it is possible for doctors to prescribe a cannabinoid at present, Nabilone, which is licensed for the treatment of nausea and vomiting associated with cancer therapy. The availability of this drug means that doctors can use it for the treatment of other conditions if a responsible body of medical opinion would support the practice. The BMA's recent report on the therapeutic use of cannabinoids would suggest to me that such a body of opinion does exist for the medical conditions they suggested cannabinoids to be useful for. Therefore needy patients can be offered cannabinoid treatment at present without any change in the law. Also research in this area is possible.

2. Cannabinoids exacerbate psychosis, especially schizophrenia. This is a significant clinical problem and if you wished to speak to an expert who has recently reviewed this field I would suggest Professor G Harrison, Division of Psychiatry, University of Bristol. Also some very new data from the USA where cannabinoid infusions are given to schizophrenics in a controlled scientific manner shows a clear worsening. These findings are as yet unpublished but being presented in a meeting I am helping to run in Glasgow in July.

3. Please note that cannabis acts at a receptor in the brain. These receptors are present in high numbers and it seems almost certain there exist natural (endogenous) substances that act on these. Cannabis and related compounds are agonists, ie they turn on the function of the receptor, just as the natural substances do. Several antagonists of this receptor are now available. They may have important therapeutic potential, eg in the treatment of schizophrenia, and clinical trials are underway. In any statement about cannabinoids it will be important to distinguish between agonist and antagonist cannabinoids.

I hope these comments are of help and I would be happy to discuss them further. Best wishes.

22 April 1998

#### **Supplementary Memorandum by Dr Roger Pertwee**

I am writing in reply to your question of whether anyone has yet tried therapeutic applications of the endogenous cannabinoid, anandamide.

As far as I know, anandamide has never been given to human subject/patients. However, anandamide is known from *in vivo* and *in vitro* animal experiments to share many of the pharmacological properties of other cannabinoid CB<sub>1</sub> receptor agonists (eg delta-9-THC). These include the ability to induce antinociception (analgesia) and antihyperalgesia, although surprisingly there is some evidence in the literature that the antinociceptive effect of anandamide is not blocked by the CB<sub>1</sub> receptor antagonist, SR141716A (which does block the antinociceptive and antihyperalgesic effects of other CB<sub>1</sub> receptor agonists). Since anandamide has other cannabinoid properties (eg it is known to lower intra-ocular pressure in animals, it is likely that it shares the therapeutic potential of other cannabinoids. It is also possible that drugs which modulate endogenous levels of anandamide through effects on anandamide tissue uptake or metabolism have therapeutic potential. 2-arachidonoyl glycerol, another endogenous cannabinoid, has also been shown to be antinociceptive in animals.

6 July 1998

#### **Memorandum by the Royal College of General Practitioners**

1. The Royal College of General Practitioners welcomes the opportunity to present a preliminary paper to the Inquiry into Cannabis, specifically the scientific arguments for and against relaxing rules on medical and recreational use.

2. We note recent events which have presumably contributed to the setting up of this inquiry; these seem to have included *The Independent* newspaper's campaign for the decriminalisation of cannabis, the BMA



report on the medical use of cannabis and the supposedly suppressed report from the USA leaked in New Scientist recently. We also understand that there has been a document prepared by the Department of Health following suggestion by the Advisory Council on the Misuse of Drugs that this was an important area for clarification. It does seem that there is a lot of information around which has not been made available for public scrutiny or for debate within the medical profession. This has undoubtedly led to confusion and some anxiety. We therefore welcome the proposed inquiry which should help clarify matters through a formal process of taking evidence and considering the various issues.

3. There seem to be a number of quite different strands. The BMA document was principally about the medical uses of cannabis and its derivatives and this matter has been considered recently by Parliament when making a decision to allow the use of THC (marketed as marinol) for the use of patients suffering from nausea due to advanced cancer or chemotherapy. Another significant strand in the medical arena is the use of cannabis for patients with multiple sclerosis and similar conditions. These are quite separate to the debate on the recreational use of cannabis—which seems, at least in political terms, the more difficult question. Cannabis use is clearly widespread and increasing in the UK and this must cause some anxiety to government.

4. It seems likely that cannabis will have some dangers and side effects, either directly as a toxin or indirectly as inducing behavioural problems requiring control in areas such as public behaviour, work practice, driving, etc. On the other hand, the suggestion that it is less dangerous than alcohol and nicotine is probably quite true.

5. It does seem that there are a number of experts in the field. We are aware of legitimate researchers, including those in primary care, have often been frustrated by the difficulty in accessing appropriate research funds to do behavioural research in this contentious area.

6. The RCGP Scientific Foundation Board has funded a small project to investigate the extent of cannabis use in a general practice. I would be happy to arrange for a copy of this report to be sent to the inquiry. There does seem to be a need for more research based in primary care to look at medium to long term use of the medical effects of cannabis—perhaps looking at both confirmed drug users and controls. Such a study could be very useful in helping clarify an area which is still unclear, namely the cumulative effects (such as respiratory disease and cardiovascular disease) and acute community crises (mainly psychological) caused by cannabis use. The Royal College of General Practitioners would certainly encourage research in the community and we would draw attention to the dangers of relying upon the unevaluated opinion prevalent at the present time.

7. We understand that there is a series of monographs from the Australian Drugs Task Force which look into the legislative options for cannabis in Australia, the psychological consequences of cannabis use, and the harmful effects of cannabis and to draw attention to the many unanswered questions and the poor studies available in most areas.

8. Much of the research is based on American data from the 1970s and 1980s and there is a need for contemporary data. Quantities in use today tend to be more excessive than in the past and therefore older studies are less valuable in evaluating side effects. It seems likely that the reason for more excessive use today is easy availability, principally brought about by the type of forced growth, carried out in all countries, of the stronger varieties. There does seem to be a close connection with other drugs of abuse, particularly nicotine and alcohol.

9. I trust this information is helpful—please do not hesitate to contact me again should you wish clarification of the issues I have raised. We look forward to helping the inquiry in any way that we can.

*Dr Bill Reith*

Honorary Secretary

8 May 1998

#### **Memorandum by the Royal College of Psychiatrists**

The Royal College of Psychiatrists welcomes the opportunity to contribute to the House of Lords enquiry.

This response was prepared by a working group led by Dr Andrew Johns; membership of which is given in Annexe C. (*not printed*)

This response has been endorsed by the President of the Royal College of Psychiatrists.

#### **PSYCHIATRIC EFFECTS OF CANNABIS**

##### *Introduction and remit*

The working group, in formulating its response considered the following questions posed by the House of Lords Select Committee.

1. What are the physiological effects (immediate, long-term and cumulative) of taking cannabis, in its various forms?

2. What are the psychological effects?
3. How do these effects vary with particular methods of preparation and administration?
4. To what extent is cannabis addictive?
5. To what extent do users develop tolerance to cannabis?
6. What is the evidence that cannabis in its various forms has valuable medicinal actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?

On the basis of the answers to these questions,

7. How strong is the scientific evidence in favour of permitting medical use?
8. How strong is the scientific evidence in favour of maintaining prohibition of recreational use?

### *Scope and structure of this review*

Although the use of cannabis is generally described by users as pleasurable, there is good evidence for a wide range of adverse mental effects. These include effects on mood, impairment of perception, memory, and judgement, and the risk of dependence, mental illness and worsening of pre-existing mental illness.

This review will summarise the evidence for the prevalence and nature of untoward mental effects of cannabis and consider the public health implications of these findings. Where the use of technical terms cannot be avoided, an explanation is provided.

This review will not deal with the general physiological effects of cannabis, or with the general psychological effects of the drug, or with the evidence for medical use, as it is understood that these issues are covered in separate submissions to the Select Committee.

The main findings are presented in summary form and all of the evidence cited can be found in Appendix A (*not printed*).

### *Summary of main findings*

The untoward mental effects of cannabis may be classified:

1. Acute psychological responses such as panic, anxiety, depression or psychosis. These effects may be described as toxic in that they are generally due to excess consumption of the drug.
2. Effects of cannabis on pre-existing mental illness and cannabis as a risk-factor for developing mental illness.
3. Dependence, tolerance and withdrawal effects.
4. Cognitive effects ie on learning and memory.

#### 1. Acute adverse psychological effects

1.1 It is not uncommon for cannabis to lead to acute adverse mental effects. Generally speaking, these effects are dose-related and worsen with continuing or increasing consumption. It is difficult to predict the risk of adverse effects for any particular user, but constitutional factors such as relative youthfulness, personality and vulnerability to mental illness lower the threshold for adverse effects.

1.2 *Psychological symptoms*: about 20 per cent of cannabis users describe psychological symptoms such as panic, anxiety, low mood, feelings of persecution, tiredness and low motivation (Thomas 1996, Troisi et al 1998, Reilly et al 1998). Psychotic reactions are not uncommon; about 15 per cent of cannabis users may report symptoms such as hearing voices or having unwarranted feelings of persecution (Thomas 1996).

1.3 *Toxic confusional state*: in high doses, cannabis can induce a toxic psychosis with mild impairment of consciousness, distorted sense of time, and dreamy euphoria progressing to fragmented thought and hallucinations. This can be accompanied by panic, irrational fears, and in consequence, agitated or disturbed behaviour with limited insight. These symptoms generally resolve within a week and amnesia for the episode of disturbance is common. (Lishman 1998, Talbot & Teague 1969, Chopra & Smith 1974, Tennant & Groesbeck 1972, Chaudry et al 1991).

1.4 *Acute functional psychosis*: cannabis can also induce an acute functional psychosis which is a state resembling the symptoms of acute schizophrenia without the confusion and memory impairment of the toxic psychosis. This generally resolves within a week. (Thacore & Shukla 1976, Rottanburg et al 1982, Tsuang et al 1982, Mathers & Ghodse 1992).

1.5 *Impact*: the ability of cannabis to cause profound but relatively short-lived changes of mental state is of considerable social and clinical importance. The disturbed behaviour which may accompany these toxic states can have untoward personal consequences and affect the family of the user and society in general. Although the precise prevalence is unknown, it is probable that toxic states due to cannabis lead to a considerable number of urgent psychiatric consultations and admissions, especially in inner-city areas.



## 2. Effects of cannabis on mental illness

2.1 There is strong evidence that cannabis has an adverse effect on pre-existing mental illness and some research which suggests that cannabis is a risk-factor for mental illness.

2.2 A high proportion of regular users of cannabis are found to have additional mental health problems, generally alcohol misuse and depression (Regier et al 1990, Troisi et al 1998). Recent UK data indicates that patients with severe mental illness such as schizophrenia, have high rates (15 per cent) of drug misuse problems and cannabis is the most common drug of misuse (Menezes et al 1996).

2.3 Although some people with schizophrenia report that use of cannabis reduces anxiety and depression, there is good evidence that it also aggravates symptoms such as hallucinations and delusions. The use of cannabis also leads to more frequent episodes of acute illness and increased use of psychiatric services (Dixon et al 1990, Peralta and Cuesta 1992, Negrete et al 1986, Baigent et al 1995).

2.4 There is some evidence that the heavy use of cannabis can be a risk factor for schizophrenia, but only in a minority of cases (Andreasson et al 1987).

2.5 Some cannabis users report "flashbacks" or fleeting partial re-experiences of the acute drug effects which may occur for a considerable time after cessation of use (Thomas 1993).

2.6 It has been suggested that cannabis causes an amotivational syndrome with marked lassitude and lack of motivation, but this almost certainly represents nothing more than ongoing intoxication in frequent users of the drug (Negrete 1986).

2.7 The effects of cannabis on patients with severe mental illness are also of considerable personal and clinical and psychological importance. It may be concluded that misuse of substances such as cannabis is one of the main factors leading to relapse among schizophrenic patients in the community.

## 3. Cannabis dependence

3.1 Cannabis dependence is the preferred term for an addiction to cannabis. Cannabis use can lead to tolerance in which giving the same dose over time has a lesser effect or, an increasing dose is needed to produce the same effect. A cannabis withdrawal syndrome has been described comprising restlessness, anxiety, low mood, insomnia and minor physical symptoms (Georgotas and Zeidenburg 1979, Jones and Benowitz 1976, Nahas 1984, Mendelson et al 1984, Pertwee 1991).

3.2 The prevalence of cannabis dependence in regular users is about 20 per cent (Wiesbeck et al 1996, Thomas 1996). The risk of dependence has been estimated at about 20 per cent for those individuals using cannabis more than five times and at about 10 per cent for those who have "ever" used the drug (Hall et al 1994).

3.3 Men appear to have higher rates of cannabis related problems, than women (Anthony & Heltzer 1991).

## 4. Cognitive effects of cannabis

4.1 There is some evidence for some long-term adverse effects of cannabis on cognition, but these are not easy to detect and may not have much effect on everyday functioning. However, adolescents who take cannabis may be particularly at risk of memory impairment. There is no evidence that cannabis causes structural brain damage (Hochman & Brill 1973, Schwartz et al 1989, Solowij et al 1991, 1995, Fletcher 1996, Lishman 1998).

## 5. Vulnerability to adverse effects of cannabis

5.1 Adolescents may be particularly vulnerable to the adverse effects of cannabis, including toxic states, and impaired learning and memory (Hall et al 1994, Newcombe and Bentler 1988, Schwartz et al 1989). Indeed, vulnerable individuals may be drawn to early onset use (Fergusson and Horwood 1997). Clinical experience suggests that cannabis users who also misuse other drugs and alcohol appear to experience more severe mental health problems and there is also a tendency for young people to misuse a range of drugs in addition to cannabis.

## 6. Cannabis, mental illness and violence

6.1 Cannabis dependence appears to be associated with an increased risk of violent behaviour, but this is not a clear-cut relationship or its only cause. Given that misuse of drugs such as cannabis by patients with serious mental illness is one of the main triggers for relapse, then cannabis misuse may be one factor aggravating aggressive behaviour in these patients (Swanson et al 1990, Johns 1997, Scott et al 1998).

## 7. Public health implications of these findings

7.1 A significant percentage of users will experience short-lived adverse mental effects. These include anxiety, depression, and also paranoia (persecutory feelings) and psychosis (hallucinations and delusions). It may be suggested that these short-lived effects are essentially trivial and self-limiting. However, not only can such symptoms precipitate further use, but they present as acute mental illness with personal distress, irrational behaviour and the possibility of harm to self or to others.

7.2 The risk of developing cannabis dependence among regular users is not insignificant, it may even represent the same order of risk as that of alcoholism among regular drinkers ie approximately 5 per cent of the population. Cannabis dependence does not appear to be associated with the same morbidity and mortality as alcoholism or heroin addiction, but runs the risk of major interference with personal competence and disruption of work and family life. The physical health risks of cannabis eg respiratory disorders will clearly be increased in cannabis dependent individuals.

7.3 Individuals with severe or chronic mental illnesses such as schizophrenia are especially vulnerable to the adverse effects of cannabis. It is probable that misuse of cannabis provokes relapse and aggravates existing symptoms. This is of especial concern given that "care in the community" policy means that the majority of patients with severe mental illness are not accommodated in psychiatric institutions, and so have the same increased availability of illicit drugs, as the host population. Furthermore, misuse of drugs such as cannabis is one of the main risk factors for relapse and violent behaviour in severe mental illness. It must be a high priority for the medical profession to appreciate the risk to the mentally ill posed by drugs such as cannabis and to work with patients in order to ensure that the risks of cannabis use are minimised. Similar arguments apply to the welfare of patients with mental illness in prisons and psychiatric hospitals, where there is an urgent need to prevent the misuse of drugs such as cannabis which can aggravate symptoms and delay recovery.

7.4 For these reasons it may be concluded that any increase in absolute population levels of cannabis consumption will lead to an increase in psychological morbidity, as summarised above.

### **Memorandum by the Royal Pharmaceutical Society of Great Britain**

#### **SUMMARY OF RECOMMENDATIONS**

##### *Recommendation 1*

In any future deliberations about cannabis and cannabinoids, discussions about the possible medical use should be divorced entirely from discussions about possible recreational use.

##### *Recommendation 2*

Strong encouragement should be given to the conduct of additional clinical trials on the medical use of dronabinol, particularly for the symptoms of multiple sclerosis.

##### *Recommendation 3*

Encouragement and support be given to the conduct of research into the medicinal use of cannabinoids, either given singly or in combinations (including standardised preparations of cannabis), by routes other than by smoking, for intractable pain and especially in terminal illnesses.

##### *Recommendation 4*

Encouragement and support be given to the conduct of further research into the pharmacological basis for the actions of cannabinoids, and the development of novel synthetic cannabinoids as licensed medicines which meet current safety and efficacy criteria.

##### *Recommendation 5*

The government should consider ways in which support can be given for clinical research into the potential therapeutic use of cannabinoids, especially for the medical conditions listed under Paragraph 4 (qv).

##### *Recommendation 6*

The government should consider making changes in the classification under the Medicine Act 1968 and the Misuse of Drugs Regulations 1985 (as amended) to remove the cannabinoids from Schedule 1 and place them in Schedule 2. This will mean that cannabinoids are subject to the same levels of control as apply to (for example) morphine, without the requirement for the issue of a licence by the Home Office for use in the conduct of clinical trials.



## 1. PREAMBLE

1.1 The Royal Pharmaceutical Society is incorporated by Royal Charter as the registration and professional body for pharmacists in Great Britain in all aspects of practice of the profession, and the promotion of pharmaceutical education and the application of pharmaceutical knowledge. The Society welcomes the opportunity to respond to the invitation of the Sub-committee II of the Science and Technology Committee to submit evidence on the medical use of cannabinoids.

1.2 The Royal Pharmaceutical Society has undertaken to present evidence to the Committee to help answer the question on the possible medical use of cannabis and cannabinoids. At this time, it does not offer a view on the continuance of the prohibition on recreational use. Indeed, it is of the view that the two issues should not be considered concurrently.

### *Recommendation 1*

In any future deliberations about cannabis and cannabinoids, discussions about the possible medical use should be divorced entirely from discussions about possible recreational use.

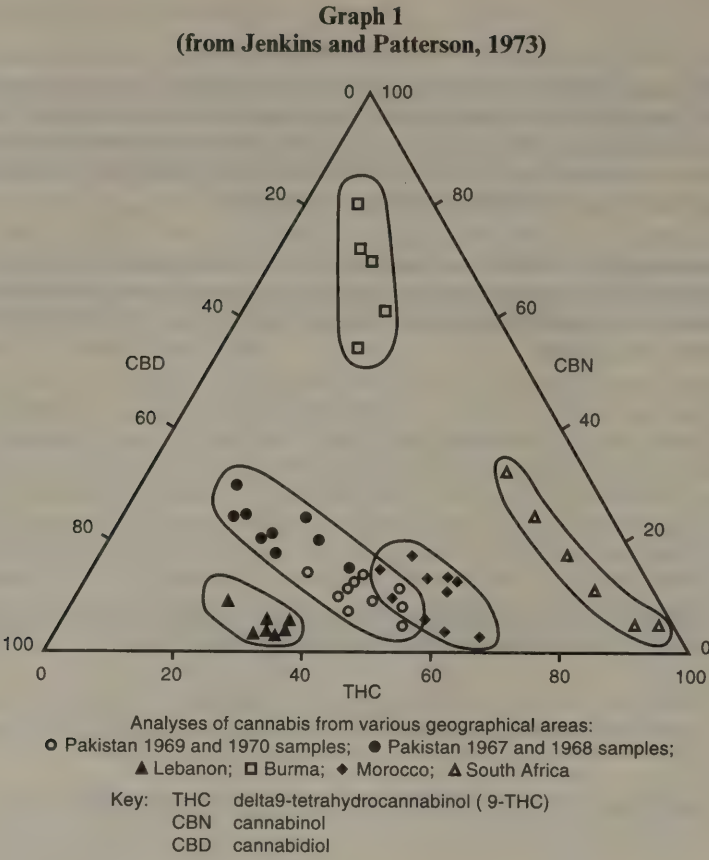
## 2. THE MATERIAL

2.1 Cannabis is obtained from the plant *Cannabis sativa*. Cannabis plant material—the leaves, flowering tops and resin exudate—is prepared (for “recreational” use) in a variety of forms, which are known by various “street” names. This material is of variable and un-regulated quality. The active components of cannabis are the cannabinoids which are relatively low molecular weight compounds (about 300 daltons) found only in the Cannabis genus. There are about 60 cannabinoids present in cannabis; most of these are present in very small proportions and their pharmacological and therapeutic actions are unknown. The main constituent is delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) but other components are delta-8-tetrahydrocannabinol ( $\Delta^8$ -THC), cannabiniol, cannabidiol, and cannabichromene are all present in sufficient quantities to be extracted, purified and studied. Also, two metabolites of the cannabinoids, 11-hydroxy- $\Delta^9$ -THC and (-)- $\Delta^8$ -THC-11-oic acid, have been studied for psychoactivity.

2.2 Cannabis was introduced into Europe by O'Shaughnessy, an Irish surgeon, in 1842, for use in such conditions as the relief of pain, muscle spasm, convulsions in tetanus, rabies, rheumatism and epilepsy. Cannabis was subsequently used for these and a range of other conditions, including its action in increasing uterine contractions in child-birth. Usage subsequently declined, probably because of the unsatisfactory nature of the available preparations, the variation in potency, irregularity in absorption after oral administration, doubt about the optimum dose regimen, the slowness of action, and its narcotic properties. Cannabis was dropped from the 1932 British Pharmacopoeia but Cannabis, Cannabis Extract and Cannabis Tincture were all official in the British Pharmaceutical Codex 1949. Cannabis Extract is an alcoholic extract of Cannabis BPC prepared from Cannabis BPC by percolation. Cannabis Tincture BPC is prepared by dilution of Cannabis Extract BPC and the monograph specified standards for alcohol content and density (weight per millilitre); however, there was no standard for either the total content of cannabinoids or the proportions of individual cannabinoids. Prior to 1971, Cannabis Tincture was available for prescription by British GPs. Details of Cannabis Extract and Cannabis Tincture are given in Appendix 1.

2.3 With the elucidation of structures and the synthesis of cannabinoids over the period 1940 to 1965, there was renewed interest in these compounds. These studies opened up the possibilities for the preparations of standardised preparations of naturally-occurring cannabinoids and of synthetic cannabinoids with selectivity of action.

2.4 The unsatisfactory nature of the naturally-occurring materials has been demonstrated by research on the variability of content of cannabinoids in cannabis. Studies by Jenkins and Patterson (1973) on material (from Customs seizures) from various countries of origin analysed for THC, cannabidiol (CBD) and cannabiniol (CBN) showed very large variations.



Graph 1 shows the content of these three components in the samples. In this study, samples from South Africa (for example) were found to be particularly rich in THC. This finding emphasises the need to conduct clinical studies on preparations that have been standardised for cannabinoid content, or on single cannabinoids, and not on preparations with uncertain composition.

2.5 In addition, a number of cannabinoids have been synthesised and two of these are licensed for medicinal use, namely nabilone, in the UK, and dronabinol (which is synthetic  $\Delta$ 9-THC), in the USA. Dronabinol may be prescribed in the UK on a named-patient basis for the control of nausea and vomiting induced by anti-cancer agents.

3. POSSIBLE INDICATIONS FOR THE USE OF CANNABINOIDS

The list of clinical conditions for which reports exist of beneficial treatment with cannabis include the following:

- muscle spasticity;
- nausea and vomiting;
- pain;
- anorexia;
- epilepsy;
- glaucoma;
- bronchial asthma.

4. EVIDENCE FOR ACTIVITY OF CANNABINOIDS

Although cannabis and cannabinoids have been recommended for treatment of a range of clinical conditions, the Society believes that the efforts to establish or refute efficacy should focus on those indications where there is the best evidence of activity and where alternative treatments are not available or of limited use. These indications are muscle spasticity, nausea and vomiting induced by chemotherapy regimes, pain, and anorexia.



#### 4.1 Muscle Spasticity

Muscle spasticity, tremor, pain and nocturia are the most common effects of multiple sclerosis. Many reports have appeared in newspapers of the palliative effects of cannabis. In animal experiments, cannabinoid receptor agonists have been shown to suppress spinal reflexes, and THC has been demonstrated to delay and reduce the intensity of disease in an experimental model of multiple sclerosis. In a survey amongst 112 patients with multiple sclerosis, the percentages of these patients who reported improvements in spasticity at onset of sleep, pain in muscle, spasticity on awakening at night, pain in the legs at night, tremor in arms and/or head, and depression, were found to be between 90.6 per cent and 96.5 per cent (Consroe et al, 1997).

Very few clinical studies have been reported. Group sizes are small and no recent studies were revealed in the literature search that was conducted for the purpose of compiling this evidence. Petro and Ellenberger (1981) presented evidence for the effect of oral  $\Delta$ 9-THC on spasticity in nine patients in a double-blind study. The patients received a capsule containing either 10 mg or 5 mg of THC, or placebo. The clinician (blinded to the treatment) observed the patient before and at 1.5 hour intervals after administration. Measurements were made of deep tendon reflexes, muscular resistance to stretch in the legs, and abnormal reflexes on a scale of 0 to 4, to give a "spasticity score". For the group, 10 mg of THC significantly reduced spasticity by clinical measurement; the improvement occurred in a time-dependent manner, with maximum effect at 3 hours post-administration. However, only three of the nine felt that their condition had improved.

Ungerleider et al (1988) noted significant subjective improvements, compared with a placebo, in all 12 patients with multiple sclerosis after treatment with 7.5 mg of oral  $\Delta$ 9-THC but these were not accompanied by changes in the relevant objective measurements and patients did not request further treatment with THC.

#### Recommendation 2

Strong encouragement should be given to the conduct of additional clinical trials on the medical use of dronabinol, particularly for the symptoms of multiple sclerosis.

#### 4.2 Nausea and Vomiting

A number of papers report on the efficacy of  $\Delta$ 9-THC (or dronabinol) in comparisons with other anti-emetics (haloperidol, metoclopramide, prochlorperazine), in the treatment of nausea in patients who have received chemotherapeutic agents for the treatment of cancer. Study designs were all similar, with randomised double-blind comparisons of a single dose level of THC (usually 15 mg) and a "standard" anti-emetic drug; both were given orally, before administration of the chemotherapeutic agent and then at six to eight hour intervals thereafter.

Ekert et al (1979) reported that  $\Delta$ 9-THC was significantly better than metoclopramide in prevention of nausea and vomiting in children but that not all patients obtained relief from THC.

Sallan et al (1980) conducted a study of  $\Delta$ 9-THC specifically in patients who had not responded to standard anti-emetic therapy and concluded that "THC is an effective anti-emetic in many patients who receive chemotherapy for cancer and for whom other anti-emetics are ineffective". In this study THC gave more complete responses (prevention of nausea and vomiting) in about half of the patients, compared to prochlorperazine with about a quarter of patients responding.

Abrahamov et al (1995) have reported on the efficacy of  $\Delta$ 8-THC (which is less psycho-active than  $\Delta$ 9-THC) as an anti-emetic in eight children between three and 13 years old prior to treatment with an anti-cancer agent. Originally planned as a comparative study with metoclopramide, the study continued with only the treatment with the cannabinoid because of its superior efficacy. This study is important because it demonstrates efficacy in a compound with lower psychoactivity than that of  $\Delta$ 9-THC and thus not attributable to psychoactive action.

The review article by Voth and Schwartz (1997) lists the studies on the comparative efficacy of THC over the period 1975 to 1991 and the results are summarised in Table 1.

The review article of Ashton (1997) concluded that cannabinoids are effective as anti-emetic agents in the treatment of vomiting induced by anti-cancer drugs and their activity is similar to, or better than, the older drugs. This does not appear to be an area of current research activity and no papers on the anti-emetic activity of  $\Delta$ 9-THC have been identified post-1991 which either support or refute this conclusion. Consequently, no studies appear to have been reported on efficacy compared with the newer anti-emetic agents, such as odansetron and the other 5-HT<sub>3</sub> antagonists. In addition, the adverse effects of  $\Delta$ 9-THC may limit its use in this indication. The place of THC, particularly in the treatment of delayed-onset emesis (> 24 hours post treatment) can only be defined more clearly through further clinical trials.

The results from the single study on  $\Delta$ 8-THC activity (Abrahamov et al, 1995) look encouraging and here too these studies need to be extended to other patient groups and efficacy compared to the 5-HT<sub>3</sub> antagonists.

It remains to be established if synthetic cannabinoids can be produced which retain an anti-emetic action without a psychoactive effect.

### 4.3 Pain

Many analgesics are available for pain relief and the “pain ladder”, where the strength of the analgesic is progressively increased to meet the needs of the condition is well established.

Noyes et al (1975a) demonstrated significant pain relief in patients with cancer pain by treatment with 15 and 20 mg oral  $\Delta^9$ -THC in a double-blind, placebo controlled study in 10 patients. In a subsequent study (Noyes, 1975b), efficacy was compared with oral codeine (60 and 120 mg). Pain relief was similar for the two treatments.

Further evidence for analgesic activity has been provided in a double-blind, placebo-controlled study in a patient with spinal cord injury (Maurer, 1990), and in a group of 56 patients with post-operative pain who were treated with intramuscular levonantradol, a synthetic cannabinoid (Jain et al, 1981).

In contrast, no analgesic effect was observed in 10 patients undergoing dental surgery treated with intravenous bolus injection of THC (Raft et al, 1977) and in 10 patients with chronic neuropathic pain given oral cannabidiol (Lindstrom et al, 1987).

A number of anecdotal reports have appeared which describe pain relief. Dunn and Davis (1974) describe the use of THC in phantom limb pain—which is recognised as being particularly difficult to treat. Grinspoon and Bakalar (1993) document the use of cannabis in one patient with a brain tumour, in two with rare painful conditions and alleviation in one patient with migraine.

More importantly, the identification of both central and peripheral cannabinoid receptors and their own naturally-occurring ligands, provides a sound basis for understanding the mode of action of cannabinoids, both natural and synthetic. The central pain-relieving effects of cannabinoids have been well documented. Peripheral cannabinoid receptors are to be found in many organs, notably the spleen and the lymph nodes, and their activity may have an important role in the inflammatory process that leads to pain.

In a recent paper Holdcroft et al (1997) reported the pain management of a patient with a 10-year history of chronic relapsing pain and inflammation of gastrointestinal origin (diagnosed as familial Mediterranean fever). Treatment was with capsules of cannabis oil, standardised on THC content. The study showed that the demand for morphine (as the escape analgesic) was substantially lower during a period of active treatment with cannabis oil, compared to a period of placebo treatment.

There are a number of conditions which are not amenable to available medicines and which maybe alleviated in some patients by treatment with cannabinoids. The evidence, although slim, does show that in some conditions (but not all) cannabinoids have an analgesic activity, and there is an underlying pharmacological basis for their action, supported by the results of studies in laboratory animals. Consequently, further studies are required to try to define which of these conditions cannabinoids can effectively treat.

### Recommendation 3

Encouragement and support be given to the conduct of research into the medicinal use of cannabinoids, either given singly or in combinations (including standardised preparations of cannabis), by routes other than by smoking, for intractable pain and especially in terminal illnesses.

### 4.4 Anorexia

Cannabis has been advocated to treat anorexia but here too the evidence is equivocal. The strongest evidence of activity is found in patients with AIDS and this may be due, in part at least, to the anti-emetic effects of THC. The open-label study in 10 patients with AIDS-related illnesses by Plasse et al (1991) showed that administration of oral THC (as dronabinol) converted a median weight loss of 0.93 kg/month before treatment to a weight gain of 0.54 kg/month over a 5-month period. In the larger study by Beal et al (1995), 72 patients with advanced AIDS-related illnesses received oral THC (as dronabinol) or placebo. It was found that dronabinol, but not placebo, significantly reduced nausea, prevented further weight loss and improved patients' mood. On the basis of these results, the US Food and Drug Administration has licensed the product for anorexia associated with AIDS.

### 4.5 Epilepsy

Carlini and Cunha (1981) reported on studies with cannabidiol in a group of patients with secondary generalised epilepsy, refractory (resistant) to known anti-epileptic drugs. In eight patients receiving 200 or 300 mg cannabidiol daily for a period of up to 4.5 months, seven were assessed to have an improvement, compared to one patient on placebo who showed improvement.



## 5. HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF PERMITTING MEDICAL USE?

5.1 The evidence for the medical efficacy of cannabis for all the putative indications listed above is based on anecdote, case reports or relatively small studies. It is disappointing that the clinical and scientific community has not undertaken or commissioned larger, well-constructed studies to date. This is attributed to the following:

- a “stigma” attached to the conduct of trials with an “illicit” substance;
- the additional burden on researchers to obtain a licence from the Home Office to conduct research in the UK; and
- the inability by the pharmaceutical industry to obtain any return on investment on this (or any other “orphan” drugs).

5.2 Overall, the body of evidence, although small, points to efficacy of cannabinoids and the need to encourage research into the role of standardised cannabinoid preparations and synthetic cannabinoids in the treatment (in particular) of muscle spasticity, emesis in cancer chemotherapy, pain, and anorexia associated with AIDS. It is hoped that some guidance on the conduct of clinical trials in these difficult areas will be forthcoming from the Royal Pharmaceutical Society’s clinical cannabinoid working group, recently established under the chairmanship of Professor Sir William Asscher, former Chairman of the Committee on Safety of Medicines.

### *Recommendation 4*

Encouragement and support be given to the conduct of further research into the pharmacological basis for the actions of cannabinoids, and the development of novel synthetic cannabinoids, as licensed medicines which meet current safety and efficacy criteria.

### *Recommendation 5*

The government should consider ways in which support can be given for clinical research into the potential therapeutic use of cannabinoids, especially for the medical conditions listed under Paragraph 4 (above).

## 6. ADVERSE EFFECTS

Reported adverse effects of THC administration have included “highs”, dry mouth, ataxia, visual disturbances and drowsiness (Ekert et al, 1979, Sallan et al 1980), Frytak et al (1979) reported that “THC therapy resulted in overall more unpleasant treatment than that noted with prochlorperazine or placebo”. Future clinical trials should be carefully designed to collect further data on adverse effect.

## 7. TOLERANCE

7.1 There appears to be very little scientific evidence to establish whether or not tolerance develops to the clinical effects of cannabis or cannabinoids; the few clinical studies that have been conducted have looked only at short-term effects.

7.2 Jones and Benowitz (1976) showed that tolerance developed in normal subjects to the effect of cannabis on a number of signs, including mood, heart rate, blood pressure, salivary flow, intraocular pressure, ECG changes and psychomotor performance.

7.3 More recently, Holdcroft et al (1997) reported the efficacy of standardised cannabis oil in the treatment of chronic pain to be much reduced during the last 2 weeks of a 6-week study. Ethical considerations prevented a challenge with a higher dose of cannabis oil, which would be needed to confirm that tolerance had occurred.

7.4 With the paucity of data, no firm conclusions can be drawn. The possible development of tolerance is insufficient a reason not to continue clinical studies on cannabinoids. Clinical trials should be designed to try to answer this question

## 8. ADDICTION

No information has been found in the recent literature that indicates whether cannabis is addictive. Clearly this is a concern if cannabinoids are to be used in chronic conditions over extended periods, as for multiple sclerosis. In some other putative indications for cannabis and cannabinoids, addiction is not seen to be a problem; the treatment of pain in patients with terminal cancer is an example.

## 9. QUALITY AND SAFETY ISSUES

9.1 The Society does not support the use of cannabis *per se* in non-standardised form for medicinal use. There is no basis for the use of cannabis by smoking. There is evidence that the smoking of cannabis causes pulmonary hazards which exceed those caused by tobacco (Wu et al, 1988). In a comparative study in 15 men who were habitual smokers of both cannabis and tobacco, the relative burden to the lungs of tar and carbon monoxide was measured on two occasions, after smoking a single tobacco cigarette and after a single cannabis cigarette. As compared to smoking tobacco, smoking cannabis was associated with nearly a five-fold greater increment in carboxyhaemoglobin (a measure of carbon monoxide intake) and approximately a three-fold increase in the quantity of tar inhaled, with retention in the respiratory tract of about one third more tar in the lungs. The authors conclude that smoking cannabis results in a substantially greater burden of carbon monoxide and tar than smoking a similar quantity of tobacco. The difference in levels may be due in part to different smoking "techniques". Irrespective of the explanations, the increased tar retention may reasonably be expected to lead to a greater chance of development of carcinoma of the lung.

9.2 In order to ensure that patients receive a product that is safe and effective, any extracts of cannabis that are used in clinical trials must have been analysed and standardised to contain known concentrations of active material. However, for clinical use pharmaceutical formulations that comprise either single-component natural cannabinoids or synthetic cannabinoids are required and the development of these products by the pharmaceutical industry is strongly encouraged.

9.3 The requirements for a medicine are:

- The active compound must be characterised chemically and physically
- The active compound must be presented in a standardised dosage formulation
- Adequate tests must have been conducted on its safety
- Adequate controlled clinical studies must have been conducted in well-defined disease entities and efficacy demonstrated objectively
- The evidence must have been published and subjected to peer-review.

## 10. DELIVERY OF THE ACTIVE COMPOUND

10.1 Amongst users of cannabis the most common mode of administration is by inhalation from smoked material; absorption of  $\Delta^9$ -THC by this route is very rapid and extensive.

10.2 Oral administration leads to almost complete (90 to 95 per cent) uptake of THC from the gastrointestinal tract but absorption into the systemic circulation is variable and slow because of extensive metabolism during transit through the liver, so that only 10 to 20 per cent of the administered dose reaches the systemic circulation. THC is widely distributed in body tissues, with extensive uptake in fatty tissues; consequently, low levels persist over a prolonged period with the time taken for 50 per cent loss (the half-life) being 24 to 36 hours. As a result, some of the effects of THC, such as appetite stimulation, persist for 24 hours or longer, although psychoactive effects start at 30 to 60 minutes after oral administration, peak at 2 to 4 hours and last for 4 to 6 hours. Activity is also due in part to an active metabolite, 11-hydroxy- $\Delta^9$ -THC, which is present in similar concentrations to THC.

10.3 The licensed commercial product, dronabinol, which is THC dissolved in sesame oil, is suitable for oral administration. The other routes which have been advocated and which are the subject of current research include inhalers, sprays, skin patches and suppositories, and eye-drops for glaucoma. No clinically-useful intravenous formulation is available.

10.4 Because of the known adverse effects of smoking of cannabis (Van Hoozen and Cross, 1997) the Society does not advocate the use of this route of administration. However, the evidence for activity of cannabis and cannabinoids is based to some extent upon reports and studies in which this has been the route of administration, and consequently this information has been considered in formulating the response to the specific questions posed by the Committee.

## 11. THE CURRENT LEGAL SITUATION

11.1 Cannabis, cannabidiol and cannabidiol derivatives (including tetrahydrocannabinol derivatives and 3-alkyl homologues of cannabidiol or its tetrahydro derivatives), are classified under Schedule 2 of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 1985 as having no therapeutic benefit. They cannot be prescribed by doctors or dispensed by pharmacists. They can, however, be possessed for



research purposes with a Home Office licence. If the research involves a clinical trial, permission must be obtained from the Medicines Control Agency as well as from an ethics committee.

11.2 Dronabinol (synthetic  $\Delta^9$ -THC) is classified under Schedule 2 of the Misuse of Drugs Act 1971 and Schedule 2 of the Misuse of Drugs Regulations 1985 (which also includes the opiates and major stimulants) but is not licensed for use in the UK.

11.3 Nabilone is a prescription-only medicine that is licensed in the UK "for use in the treatment of nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional anti-emetics". Use of nabilone for other indications, and any use of dronabinol in the UK, constitutes unlicensed use.

11.4 Whereas it is legal for a GP to prescribe a medicine that is not licensed in the UK, or a licensed medicine for an unlicensed indication, this places additional responsibilities upon the GP, both to the patient and to the pharmacist. If unlicensed use of cannabinoids becomes prevalent (in the short term) as a result of this Inquiry, then it is essential that there be full consultation between the medical and pharmacy professions.

11.5 For the reasons given under Section 5, a change in the legal classification is required.

#### *Recommendation 6*

The government should consider making changes in the classification under the Medicine Act 1968 and the Misuse of Drugs Regulations 1985 (as amended) to remove the cannabinoids from Schedule 1 and place them in Schedule 2. This will mean that cannabinoids are subject to the same levels of control as apply to (for example) morphine, without the requirement for the issue of a licence by the Home Office for use in the conduct of clinical trials.

### **Appendix 1** **(from British Pharmaceutical Codex 1949)**

#### **EXTRACTUM CANNABIS** **(Ext. Cannab.)** **Extract of Cannabis**

|                            | <i>Metric</i>                 | <i>Imperial</i> |
|----------------------------|-------------------------------|-----------------|
| Cannabis, in coarse powder | 1,000g                        | 10 oz           |
| Alcohol (90 per cent)      | ... a sufficient quantity ... |                 |

Exhaust the cannabis by percolation with the alcohol (90 per cent) and evaporate to the consistence of a soft extract.

Storage: it should be stored in well-closed containers which prevent access of moisture.

Dose: 16 to 60 milligrams ( $\frac{1}{4}$  to 1 grain).

In making this preparation the alcohol (90 per cent) may be replaced by industrial methylated spirit diluted so as to be of equivalent alcoholic strength, provided that the law and the statutory regulations governing the use of industrial methylated spirit are observed.

#### **TINCTURA CANNABIS** **(Tinct. Cannab.)** **Tincture of Cannabis**

|                       | <i>Metric</i> | <i>Imperial</i>  |
|-----------------------|---------------|------------------|
| Extract of Cannabis   | 50g           | $\frac{1}{2}$ oz |
| Alcohol (90 per cent) | to 1,000ml    | to 10 fl oz      |
| Dissolve              |               |                  |

Standard:

Weight per ml At 20°, 0.842g to 0.852g.

Alcohol content 83 to 87 per cent v/v of ethyl alcohol.

Dose: 0.3 to 1 millilitre (5 to 15 minims).

Table 1  
Studies that used Delta-9-Tetrahydrocannabinol as an Antiemetic Agent for Patients with Cancer Receiving Chemotherapy

| Study (Reference)          | Dosage and form of THC   | Patients | Design                               | Patient Age | Results   |
|----------------------------|--|----------|--------------------------------------|-------------|---|
|                            |  | <i>n</i> |                                      | <i>y</i>    |   |
| Sallan et al (1975)        | 15mg or 10mg/m <sup>2</sup> body surface area orally every 4 hours for 3 days                | 10       | Randomized, double-blind, cross-over | 29.5        | THC better than prochlorperazine                                    |
| Sallen et al (1979)        | 10mg/m <sup>2</sup> orally every 4 hours for 3 days  | 46       | Randomized, double-blind cross-over  | 32.5‡       | THC better than prochlorperazine                                    |
| Chang et al (1979)         | 10mg/m <sup>2</sup> orally and smoked every 3 hours for 5 days                               | 15       | Randomized, cross-over               | 24†         | THC better than prochlorperazine                                    |
| Frytak et al (1979)        | 15mg orally  | 116      | Prospective, double-blind            | 61†         | THC equal to prochlorperazine and both drugs better than placebo    |
| Kluin-Neleman et al (1979) | 10mg/m <sup>2</sup> orally   | 11       | Double-blind, cross-over             | 34.6†       | THC better than placebo   |
| Ekert et al (1979)         | 10mg/m <sup>2</sup> orally compared with metoclopramide                                      | 33       | Double-blind, cross-over             | 5-19        | THC better than prochlorperazine or oral metoclopramide             |
| Lucas and Lazio (1980)     | 5-15mg/m <sup>2</sup> orally every 4-6 hours 24 hours after chemotherapy                     | 53       | Randomized, cross-over               | Adults      | THC effective   |
| Orr et al (1980)           | 7mg/m <sup>2</sup> orally every 4 hours for 3 days   | 55       | Randomized, double-blind, cross-over | 46‡         | THC better than prochlorperazine and both drugs better than placebo |
| Gralla et al (1982)        | 10mg/m <sup>2</sup> orally every 3 hours for 5 days compared with intravenous metoclopramide | 27       | Randomized, double-blind             | Adults      | Metoclopramide better than TCH                                      |
| Ungerleider et al (1982)   | 7.5-12.5mg orally  | 214      | Randomized, double-blind, cross-over | 47‡         | THC equal to prochlorperazine                                       |
| Levitt et al (1984)        | Oral THC and smoked marijuana  | 20       | Randomized, double-blind             | 54.5‡       | Oral THC better than smoked THC                                     |
| Vinciguerra et al (1988)   | Approximately 5 mg of smoked marijuana per m <sup>2</sup>                                    | 56       | Prospective, uncontrolled            | 40‡         | Smoked THC effective; no controls used                              |
| Lane et al (1991)          | 10mg oral THC plus prochlorperazine  | 60       | Randomized, double-blind             | 55‡         | Combination more effective than individual drugs                    |

† Median age      ‡ Mean age

Letter from the Clerk to the Royal Pharmaceutical Society of Great Britain

You recommend *inter alia* that cannabinoids should be moved from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations. The BMA Report says (p2) that you want doctors to “be able to prescribe cannabinoids for specific serious disorders, at least for a trial period”. I would be grateful to know, at your convenience, whether the BMA Report has got this right: as I understand it, if cannabinoids were simply moved to Schedule 2, then doctors could prescribe them (unlicensed, and on the named-patient basis) for any disorder, and without time limit. I look forward to hearing from you.

Supplementary memorandum by the Royal Pharmaceutical Society of Great Britain

The answer to your question is yes, the BMA Report is correct.

We do recognise that the effect of Recommendation 6 is, as you have pointed out, to permit the prescribing of cannabinoids for any disorder deemed to be treatable. In this regard, the Society has moved its stance from that in 1995.

I trust that this clears up the point in your letter. If it has not done so, then please call me.

With regard to the prescribing of cannabinoids, the attached table represents the situation for four cannabinoids and the basis of their use in the UK. I hope that this table is helpful to the Committee.

Concerning the Working Group on Medical Use of Cannabinoids, under the chairmanship of Sir William Asscher, I am pleased to report that the first meeting will take place later this month.

Dr J A Clements  
Head, Scientific and Technical Services

17 June 1998



|             | Prescribing of Cannabinoids |                        |   |   |
|-------------|-----------------------------|------------------------|---|---|
|             | Commercially available      | Licensed for use in UK | Subject to Misuse of Drugs Act (and current status) | Basis of use in UK  |
| Nabilone    | Yes                         | Yes                    | No  | A GP can prescribe but accepts responsibility for use for any unlicensed indications  |
| Dronabinol  | Yes (USA)                   | No                     | Yes (Schedule 2)                                    | A GP can prescribe on named patient basis but accepts responsibility for its use  |
| Cannabinol  | No                          | No                     | Yes (Schedule 1)                                    | If a commercial product became available and cannabinol was rescheduled to Schedule 2, a GP could prescribe but accepts responsibility for use on a named patient basis |
| Cannabidiol | No                          | No                     | No  | If a commerical product became available and was licensed, a GP could prescribe. No rescheduling is necessary   |

- The two compounds that are not commercially available are included to illustrate the following points:
- (ii) If cannabinol was to be introduced as a commercially-available licensed product, then it would require to be moved from Schedule 1 to Schedule 2.
  - (ii) Cannabidiol is not included in the list of substances and products listed in Schedule 1.

Memorandum by the Royal Society and the Academy of Medical Sciences

The Royal Society and the Academy of Medical Sciences welcome the opportunity to contribute to the House of Lords enquiry into the science behind the arguments over the use of cannabis and its derivatives. This response was prepared by a working group led by Professor P. J. Lachmann; the full membership is given at Annex A. This response has been endorsed by the Council of the Royal Society and by the Council of the Academy of Medical Sciences.

1. INTRODUCTION

In formulating this response, we considered the questions posed by the House of Lords Select Committee on Science and Technology which were outlined in the Call for Evidence. The full scientific answers to these questions are at Annex B; the evidence is summarized below. There is much anecdotal evidence regarding the therapeutic effects of cannabis, and a clear distinction needs to be drawn between evidence from these sources and evidence from controlled clinical trials and laboratory testing. In this response, we have based our arguments as far as possible on the latter.

2. WHAT ARE THE PHYSIOLOGICAL EFFECTS OF TAKING CANNABIS IN ITS VARIOUS FORMS?

The plant, *Cannabis sativa*, contains more than 60 aromatic hydrocarbon compounds called cannabinoids. Among these, delta-9-tetrahydrocannabinol (THC) is the most studied component, and synthetic compounds based on it have been produced. THC is widely accepted as being the major psychoactive component as well as being responsible for many of the pharmacological effects.

In order to have an effect a compound needs to interact with a specific receptor in the body. Two receptors, CB1 and CB2, have been identified as interacting with THC and other cannabinoids, and this is discussed fully in Annex B, although the mode of action of cannabis and its derivatives is not fully understood. Physiological effects of the cannabinoids are dependent upon whether administration is acute or chronic as well as the dose and type of administration.

Physiological effects associated with cannabis use include: reductions in psychomotor co-ordination, performance and motor function; tachycardia (raised pulse rate); lowered blood pressure on standing (at higher doses); alterations in thermoregulation, in endocrine and reproductive function and in gut motility; inhibition of neurotransmitter release; analgesia; enhanced appetite and bronchodilation.

### 3. WHAT ARE THE PSYCHOLOGICAL EFFECTS?

Psychological effects, as with physiological effects, will vary with dose and whether use is acute or chronic. A sense of euphoria is felt by regular cannabis users, intermittent users tend not to feel euphoric, but lose co-ordination instead. Higher doses of cannabis produce loss of concentration and drowsiness, and cause perceptual changes that may result in dysphoria.

Cannabis can have a marked, but short-term, effect on psychomotor performance (for example, on driving-related tasks such as reaction time). It can also affect attention and short-term memory performance (and perhaps therefore impair learning).

There is evidence for some long-term adverse effects on cognition but these are subtle and occur against a backdrop of little sign of major impairment across most of the cognitive domains investigated.

Cannabis can induce dose-related, short-term mental disturbances; effects include anxiety, panic, paranoid delusions, feelings of unreality, and distortions in perception. In the majority of instances, these disturbances are quickly recovered from and not repeated.

There is no firm evidence that long-term cannabis use induces psychiatric disturbance. Cannabis exposure has been reported to be a risk factor for schizophrenia, but causal links between the two have not been established with certainty.

### 4. HOW DO THE EFFECTS VARY WITH PARTICULAR METHODS OF PREPARATION AND ADMINISTRATION?

Cannabis is usually smoked or taken orally. Smoke from herbal cannabis contains similar toxic constituents to cigarette smoke. Oral doses give unpredictable effects due to variations between patients in absorption from the gastro-intestinal tract. More reliable formulations and modes of administration are needed; nothing approaching a pharmaceutical grade resin has ever been defined and the very large number of constituents could present major difficulties.

### 5. TO WHAT EXTENT IS CANNABIS ADDICTIVE? TO WHAT EXTENT DO USERS DEVELOP TOLERANCE TO CANNABIS?

Cannabis has a dependence potential, and evidence suggests that tolerance to both the physical and subjective effects of cannabis can occur. (One should be aware that other potentially addictive drugs with medical benefits are currently available, and these include the opioids and benzodiazepines).

Cannabis use as predisposition to later use of heroin: Suggestions are sometimes heard that cannabis may in a causal sense lead on to the taking of heroin. That in the UK a strong statistical relationship exists between prior use of cannabis and later use of heroin is undoubted, but the first drug used by people who go on to heroin is nearly always alcohol or nicotine, rather than cannabis. There is no plausible biological mechanism to support the idea of cannabis as a gateway to opiates. The dealer from whom cannabis is bought is unlikely also to be offering heroin so there is no strong explanation for linkage to be found at the social level. Thus although the idea that cannabis use can predispose to later use of heroin is difficult to disprove there is no convincing evidence to support this hypothesis.

### 6. WHAT IS THE EVIDENCE THAT CANNABIS IN ITS VARIOUS FORMS HAS VALUABLE MEDICINAL ACTIONS? IN THE TREATMENT OF WHICH DISEASES?

The active ingredient of cannabis, THC, and other cannabinoid compounds are being used to treat a variety of disorders. Drugs which selectively activate CB1 or CB2 receptors have already been developed.

*Emesis:* Dronabinol (synthetic THC in sesame oil) was approved in the US for the treatment of nausea induced by treatments such as cancer chemotherapy. In the UK, nabilone, a synthetic analogue of THC, is licensed for similar use.

*Pain:* Many currently available analgesic drugs have serious side effects and are not always effective in the treatment of pain, particularly neuropathic pain, which is resistant to the analgesic effects of opioids. Hence, there is a clinical need for the development of novel analgesic drugs. Various cannabinoids produce inhibition of pain responses. At present, there is laboratory evidence which supports an analgesic effect of cannabinoids, but there is no reliable human clinical evidence to support or refute claims of cannabinoid induced analgesia. Limited trials and anecdotal evidence suggest further clinical and laboratory study is needed. Recent work has shown that some of the analgesic effects of cannabinoids may be related to CB1 and CB2 receptors located outside the central nervous system. With further research, this could result in the development of cannabinoid analgesics which have no central nervous system side effects.

*Spasticity:* Spasticity is commonly seen in patients with multiple sclerosis, stroke, cerebral palsy or spinal injury. Animal experiments have shown that cannabinoids suppress spinal reflexes. The use of cannabinoids for multiple sclerosis and spinal injury is promising; THC significantly reduced spasticity in patients not presenting with cerebellar disease. There is much anecdotal evidence and also some limited data from controlled clinical trials that cannabinoids can reduce the intensity of some of the symptoms of multiple



sclerosis and spinal injury. However, better designed more extensive clinical trials are now needed to test these uses more conclusively.

**Glaucoma:** Raised intra-ocular pressure (glaucoma) can produce irreversible damage to the optic nerve and can cause blindness. There is good evidence that cannabinoids can lower intra-ocular pressure, although the site and optimal administration route are not yet established.

**Bronchial asthma:** Cannabinoids show promise for the treatment of the early phase response of asthma, the phase in which the small tubules in the lungs (bronchioles) narrow as a result of exposure to certain allergens. Cannabinoids can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatments. Further studies are required to improve cannabinoid formulation for administration as an aerosol.

**Appetite:** Dronabinol can be prescribed in the US as an appetite stimulant in cancer patients and to treat weight loss in AIDS patients.

## 7. HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF PERMITTING MEDICAL USE?

While there is evidence to suggest beneficial therapeutic effects from taking cannabis in relieving spasticity (particularly in multiple sclerosis), as an analgesic, as an anti-emetic, an appetite stimulant and as a bronchodilator, there is a dearth of data from randomised clinical trials. The risks and benefits of using cannabis for these various indications need to be properly evaluated for cannabis itself and for the individual cannabinoids to establish whether they have a useful role in clinical practise. Until such studies have been made, there is no persuasive case for the non-experimental medical use of cannabis.

## 8. HOW STRONG IS THE SCIENTIFIC EVIDENCE IN FAVOUR OF MAINTAINING PROHIBITION OF RECREATIONAL USE?

Our concern is only to show how science can illuminate discussion of this question rather than to put forward any particular view.

We are confident that evidence exists that cannabis use can give rise to various types of physical and psychological problems. Most individual risks, whether acute or chronic, are likely to have a dose-response relationship with level of cannabis use. Population levels of use for cannabis are likely to have a bearing on public health. Removing the prohibition on cannabis would have uncertain effects, although some harm and some added costs would undoubtedly result. The size of the impact on the nation's health cannot be inferred from reference to existing scientific evidence. It is for government to decide whether there are sufficient societal advantages to balance the risks to removing prohibition.

## 9. CONCLUSIONS

In any debate, we believe that the issues of clinical use of cannabis and its derivatives should be uncoupled from the issues of recreational use.

There is substantial anecdotal as well as a limited amount of more objective evidence that cannabinoids are clinically effective in certain conditions eg pain, spasticity and emesis. However, the effects of cannabis in various disease states may not be straightforward. Several components of cannabis might be required to reproduce the effects seen with the whole drug.

We do not consider that the current medical data on efficacy of safety from randomised controlled trials are sufficient to support the medical prescribing of cannabis as yet. This is due to the psychoactive and physiological side-effects and the evidence that tolerance and mild dependence can occur (dronabinol and nabilone, which are currently used clinically, are both psychotropic cannabinoids that probably induce tolerance and dependence). Furthermore, we do not support the notion of smoking cannabis for medical purposes; smoke from herbal cannabis contains toxic substances similar to those from cigarette smoke.

We suggest that further controlled clinical trials and laboratory research be conducted with cannabinoids under carefully defined circumstances (in whatever forms or routes of administration) and should include isolated single components of cannabis (eg THC), extracts of herbal cannabis, as well as selective CB1 and CB2 compounds. A thorough comparison of the resulting data would help to define the role of individual compounds and receptors, help to improve modes of administration and formulation, and possibly aid in the development of safer, more specific therapies for conditions that are currently poorly treated.

*E. Fellman*

*May 1998*

## ANNEX A

## Membership of working group

*Chair:* Professor P J Lachmann, FRS.

*Members:* Professor J G Edwards, CBE, Dr R G Pertwee, Professor T W Robbins, Dr A S C Rice, Sir Richard Sykes, FRS, Professor P D Wall, FRS.

*Secretariat:* Dr E Fellman.

## ANNEX B

## SCIENTIFIC EVIDENCE

1. *What are the physiological effects of taking cannabis in its various forms?*  
(By Dr R G Pertwee)

Detailed reviews of the physiological effects have been carried out by Paton and Pertwee (1973a, 1973b) and Pertwee (1988, 1997a).

1.1 The plant *Cannabis sativa* is the unique source of a set of more than sixty oxygen-containing aromatic hydrocarbon compounds called cannabinoids. Among these is  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol to which most of the known pharmacological properties of cannabis can be attributed. It is now known that the main effects of  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol are mediated by specific cannabinoid receptors, two types of which have so far been identified. These are CB<sub>1</sub> receptors, discovered in 1990, and CB<sub>2</sub> receptors, discovered in 1993. Both of these receptor types are coupled to their effector systems through G<sub>i/o</sub> proteins. CB<sub>1</sub> receptors are present in the central nervous system as well as in certain neuronal and nonneuronal peripheral tissues whereas CB<sub>2</sub> receptors are found mainly in cells of the immune system. The possibility that mammalian tissues express additional cannabinoid receptor types of physiological significance cannot be excluded. Indeed, preliminary pharmacological evidence that supports this possibility already exists. Another important recent discovery has been that mammalian tissues also produce compounds that can activate cannabinoid receptors, the most important being arachidonylethanolamide (anandamide) and 2-arachidonoyl glycerol. These "endogenous cannabinoids" and their receptors constitute the "endogenous cannabinoid system". Further details about the pharmacology of cannabinoids and their receptors can be found in a recent review (Pertwee, 1997a).

1.2 The distribution pattern of CB<sub>1</sub> receptors within the central nervous system is heterogeneous, unlike that for any other receptor type and consistent with the known ability of cannabinoid receptor agonists to impair cognition and memory, to alter motor function and movement and to relieve pain (see below). The highest concentrations of cannabinoid binding sites in the brain are in the basal ganglia (substantia nigra pars reticulata, the entopeduncular nucleus, the globus pallidus and the lateral caudate-putamen). Other areas of the brain quite rich in cannabinoid binding sites include the hippocampus, cerebral cortex, intrabulbar anterior commissure, nucleus accumbens, septum, olfactory bulb and molecular layer of the cerebellum. Among areas of the brain less densely populated with cannabinoid binding sites are the central gray substance, the area postrema, the caudal nucleus of the solitary tract, the amygdala, thalamus, habenula, preoptic area and hypothalamus, and much of the brain stem. Regions of the spinal cord that are richest in cannabinoid binding sites are lamina X and the substantia gelatinosa.

1.3 Some CB<sub>1</sub> receptors occur at central and peripheral nerve terminals and these are known to reduce transmitter release when activated. Hence one of the physiological roles of these receptors is probably to modulate the release of central and peripheral neurotransmitters in certain pathways.

1.4 Little is yet known about the physiological roles(s) of the more recently discovered CB<sub>2</sub> receptor although it seems likely that this will prove to involve modulation of immune function in health and/or disease. It is vital that further research is funded to elucidate the physiological and pathophysiological role(s) of this receptor type as this may well reveal important new clinical applications for cannabinoid receptor agonists or antagonists. Additional research is also urgently needed to establish the mechanisms underlying effects of cannabinoids of known or potential therapeutic value: it is noteworthy that almost nothing is known even about the mechanisms underlying the two effects of cannabinoids that it already is permissible to exploit for therapeutic purposes in the UK or USA: antiemesis and appetite stimulation (see below).

1.5 The effects of cannabis that make up a "high" consist essentially of changes in perception, mood, emotion and cognition. Thus, after cannabis has been taken there are reports that colours seem brighter and music more pleasant and that "felt time" passes more slowly than "clock time". Effects on mood and emotion vary. Usually there is some euphoria. Sometimes, however, particularly in the inexperienced, mood may be unaffected or there may be dysphoria or anxiety. More serious adverse psychopharmacological responses may occur, in particular panic reactions and psychoses. Signs of changed cognitive functions include difficulty in concentrating and thinking and impairment of memory. The "high" is usually followed by a period of drowsiness.

1.6 Associated with the "high" are reductions in psychomotor coordination, performance and motor function and changes in autonomic processes. The most prominent autonomic changes are cardiovascular, in particular tachycardia, postural hypotension, supine hypertension and conjunctival hyperaemia. There is



now also evidence that endothelium derived hyperpolarizing factor may be an endogenous cannabinoid—ie that one physiological role of endogenous cannabinoids may be to regulate blood flow through resistance vessels. Other changes in autonomic function that can be caused by cannabis or psychoactive cannabinoids include alterations in thermoregulation, in endocrine and reproductive function and in gut motility. More detailed descriptions of the pharmacological effects of cannabis and cannabinoids, both *in vivo* and *in vitro*, are to be found elsewhere (Paton & Pertwee, 1973a, 1973b; Pertwee, 1988, 1997a).

1.7 The part played by cannabinoid receptors in the production of some of the effects of cannabis/cannabinoids in the whole organism remains to be established. Among the effects of cannabinoids already known from animal experiments to be mediated by CB<sub>1</sub> receptors are antinociception (analgesia) and changes in memory, motor function (hypokinesia and catalepsy), thermoregulation (hypothermia), memory, gut motility (inhibition) and transmitter release (inhibition).

1.8 On repeated administration to animals or man, cannabis can give rise to tolerance and dependence. The tolerance seems to be mainly pharmacodynamic in nature, resulting far more from adaptive changes within the brain than from changes in cannabinoid disposition or metabolism. There is evidence to suggest that it stems at least in part from a decrease in cannabinoid receptor density. Cannabinoid tolerance and dependence are discussed in greater detail in section 4.

## 2. What are the psychological effects of taking cannabis in its various forms?

*Psychological (cognitive) effects of cannabis (by Professor T W Robbins)*

### 2.1 Acute effects

#### 2.1.1 Subjective and behavioural

Behavioural effects include increased tendencies to hyperactivity and laughter and talkativeness in social situations, although the discourse may not always make sense. Appetite for food and drink is enhanced. These effects are often experienced in a relatively calm, relaxed, or even dream-like subjective state, although they can be opposed by anxiety and restlessness. Sensory effects include feelings of “lightheadedness”, floating sensations, hyperacuity of visual and auditory perception, visual illusions and a marked perception of the slowing of the passage of time (Tart 1971; Grinspoon, 1977). These effects are generally dose-related and produced by the active constituent  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol. Higher doses can lead to strong feelings of panic or anxiety, paranoid reactions, and at very high doses, a state of delirium (Hollister 1986). However, the concept of a cannabis-induced state of psychosis is controversial (Thomas, 1993).

#### 2.1.2 Experimental investigations of cognitive function

Cannabis can have marked deleterious effects on psychomotor performance, for example in driving, flying aeroplanes, and the operation of heavy machinery. Even experienced users are impaired with intermediate and high doses on difficult driving-related tasks such as tracking, reaction time, and divided attention (Barnett, Licko and Thompson, 1985). Substantial deficits were seen on all measures and performance was not restored to normal levels until about 10 to 12 hours after smoking a single standardised marijuana cigarette. However, it is unlikely that cannabis at present is a major risk factor in car accidents (Gieringer 1988).

Acute cannabis has been reported to impair attentional and memory performance, when administered to cannabis experienced volunteers in the form of a standard marijuana cigarette containing  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol (THC, 1.2 per cent, by weight) (Hooker and Jones, 1987). Placebo cigarettes contained no THC but were otherwise identical, so THC can be assumed to have been the active constituent. Retrieval of lists of words in verbal free recall tasks was particularly affected by increased interference from incorrect items. The Stroop interference test of selective attention was also impaired. However, sustained attention, retrieval from semantic memory and the speed of reading and naming colours was unaffected.

There is some evidence for tolerance to acute effects on cognition in heavy cannabis smokers (Cohen and Rickles, 1974).

### 2.2 Chronic effects

#### 2.2.1 Experimental investigations of cognitive function

Users may consume cannabis on a daily basis for many years. There is evidence for some long term adverse effects but these are subtle and occur against a backdrop of little sign of major impairment across most of the cognitive domains investigated (for considered reviews, see Pope et al, 1995; Wert and Raulin, 1986). In one well-executed study, Block and Ghoneim (1993) did demonstrate that heavy marijuana use (> 7 times per week for an average of six years) in young (predominantly male) adults produced small but significant impairments in memory retrieval (Bushke test), verbal expression and mathematical ability, compared with a well-matched group of non-users. However, they also reported some small improvements in a test of concept formation at an intermediate dose. Differences in alcohol use or other, illicit drugs between these two groups were shown not to have contributed to these effects. It is possible, though unlikely, that the effects arose from residual effects of cannabis outlasting the enforced period of abstinence (24 hours). Solowij (1995) has shown deficits in selective attention and evoked potentials in ex-cannabis users, abstinent from periods of six months

to three years. Fletcher, Page and Francis (1996) also report long-term deficits in older cannabis users on certain tests of attention, involving divided or selective attention, and on short term ("working") memory tasks. They emphasise that the deficits are much more subtle than those found, for example, in dementing or amnesic disorders.

In these controlled studies there has not been information on individual differences, or gender and aged-related modulation of these effects. Nor has there been systematic analysis of the effects of modes of preparation and administration of cannabis, and its various constituents.

### 2.2.2 Relationship to brain cannabinoid receptors

The pattern of cognitive impairment described does not relate especially clearly to the distribution of cannabinoid receptors in the brain, but is by no means inconsistent with it. There has not yet been any study of the effects of the new cannabinoid receptor antagonists on cognitive function in man, although these are being developed as appetite suppressant and cognitive enhancing compounds, presumably for the treatment of dementia.

An extensive study by Kalant and colleagues (eg Stiglick and Kalant, 1982) on effects of chronic exposure to marijuana extract in rats for 90 or 180 days showed evidence of impaired spatial learning, impaired timing behaviour, hyperactivity, but enhanced avoidance learning—all symptoms associated with damage to the hippocampal formation, where cannabinoid receptor densities are high.

## 2.3 Other psychological effects (non-cognitive) (By Professor J G Edwards)

2.3.1 Cannabis is likely to produce euphoria, relaxation, a feeling of being "spaced out" and a keener appreciation of the sensory environment, and it is for those reasons that it is taken (WHO 1997). Rather easily these wanted experiences mix with or shade over toward feelings of anxiety, dysphoria and suspiciousness (WHO 1977). A few mildly bad experiences are unlikely to put the cannabis taker off continued use, but more flagrant bad experience may be a reason for quitting.

### *Short-term psychiatric mental disturbance*

Cannabis can induce mental disturbance lasting between, say, a few hours and 36 hours. Such episodes are likely to be distressing and will for this period put the user more or less out of touch with reality: the clinical picture will typically include anxiety or panic, paranoid delusions, feelings of unreality, and distortions in preception (Chopra 1974, Rottanburg 1982, Ghodse 1986, Chaudry et al 1991). Recovery is likely to be complete other than perhaps for later transient experience of flashbacks (Edwards 1983). The existence of this syndrome is well authenticated and although it is not possible to put a precise figure on the frequency of its occurrence, it is not uncommon in any country where cannabis is widely used: psychiatrists working on an emergency admission service will be alert to the existence of this syndrome (Mathers et al 1991). The condition is probably dose-related, but there may also be idiosyncratic vulnerability.

A question then arises as to the level of social concern which should attach to the potential of this drug to produce this kind of short-lived adverse event. On the one hand it should be noted that in the great majority of instances the disturbance is quickly recoverable and without sequelae. On the other hand loss of contact with reality must in principle be expected to carry some small but uncertain risk for the user and other people, and a demand on health service resources is created. To the extent that such reactions are dose-related, the dissemination of techniques of inhalation such as the "hot knives" technique which involves massive inhalation of cannabis through a funnel may carry added danger.

### *The possibility of somewhat longer term cannabis-induced psychiatric disturbance*

With chronic heavy use of this potentially cumulative drug a chronic intoxication may be induced and it is not unreasonable to expect that continuing psychotic disturbance might be an accompaniment, with the symptoms clearing only some time after the drug is stopped and while cannabis cleared from the system (Ghodse 1985). The existence of this syndrome is however only conjectural.

### *Cannabis and schizophrenia*

A Swedish study (Andreasson et al 1997) showed that at a 15 year follow-up of a cohort of young males, those who were frequent users of cannabis at base point later experienced a six-fold increase in relative risk of developing schizophrenia compared with the earlier non-users. That it a statistically significant finding, but other obvious explanations besides causality can be envisaged. The evidence that cannabis can destabilise pre-existing and otherwise successfully treated schizophrenia is more persuasive (Negrete et al 1986, Cleghorn et al 1991), and can be a matter of clinical concern for those who treat this condition.



### 3. *How do the effects vary with particular methods of preparation and administration* (By Dr R G Pertwee)

3.1 Cannabis is usually smoked or taken by mouth (as dried plant material or using the sticky resin that is secreted by the plant). Cannabis leaves or cannabis resin are sometimes taken orally in cakes or fudge or as a drink. Tincture of cannabis (a solvent extract of cannabis that it was permissible to prescribe in the UK until 1971), was of course also taken orally. The licensed medicines,  $\Delta^9$ -tetrahydrocannabinol (dronabinol) and nabilone (see section 3), are both taken by mouth.

3.2 As far as the clinical use of cannabinoids is concerned, there is a need for better formulations and modes of administration (Pertwee, 1997b). Thus when taken orally,  $\Delta^9$ -tetrahydrocannabinol seems to undergo somewhat variable absorption from the gastrointestinal tract and to have a rather narrow "therapeutic window" (dose range in which it is effective without producing significant unwanted effects) (Pertwee, 1997b). For example, in a clinical study with two multiple sclerosis patients,  $\Delta^9$ -tetrahydrocannabinol was effective in one of the patients at an oral dose of 5 mg whilst in the second patient it was effective only when the dose was raised to 15 mg (both 5 mg and 10 mg  $\Delta^9$ -tetrahydrocannabinol were ineffective in this patient). In another clinical study in which eight multiple sclerosis patients were given  $\Delta^9$ -tetrahydrocannabinol or placebo by mouth, both 2.5 and 5 mg  $\Delta^9$ -tetrahydrocannabinol were ineffective in relieving spasticity, 7.5 mg was effective and 10 mg was intolerable to some of the patients (narrow "therapeutic window"). The existence of a large inter-patient variation in the oral dose level of  $\Delta^9$ -tetrahydrocannabinol that is effective combined with a very narrow "therapeutic window" for oral  $\Delta^9$ -tetrahydrocannabinol makes it difficult to predict an oral dose of this drug that will be both effective and tolerable to a patient.

3.3 Possible alternative modes of cannabinoid administration are by rectal suppository (Brenneisen et al 1996), by skin patch, by direct application to the eye (for glaucoma) or by aerosol inhalation (see also Sections 5.4 and 5.5).

### 4. *To what extent is cannabis addictive? To what extent do users develop tolerance to cannabis?* (By Professor J G Edwards)

4.1 There is evidence that tolerance to both physiological and subjective effects of cannabis can occur in the human subject (Georgotas and Zeidenburg 1979, Compton et al 1990), and a withdrawal syndrome has been described (Jones and Benowitz 1976). Although those findings are of interest, neither induction of tolerance nor the occurrence of withdrawal symptoms are by themselves sufficient criteria to conclude that a drug has significant dependence potential in a meaningful, clinical sense. Within the present-day concept of dependence (Edwards et al 1981, American Psychiatric Association 1994), the essential question which has to be asked is whether cannabis use can lead to a strong habit, a drug-centredness, and a difficulty in giving up despite a wish so to do. That common-sense approach has then to be operationalised for purpose of research (Anthony and Hezler 1991). Seen within that kind of perspective there is now strong evidence that a clinical syndrome of cannabis dependence exists and that something between 5-10 per cent of long term cannabis users will develop dependence (see Hall et al 1994 for a review), but that figure will be influenced by dosage levels and patterns of use within any given study population. That prevalence figure is probably at rather the same level as life time prevalence of alcohol dependence among people who drink alcohol (Edwards et al 1994), but with heavier per capita use of cannabis is a higher prevalence of dependence might be expected.

4.2 The practical significance of the conclusion that cannabis has a dependence potential needs to be considered critically. Dependence is not itself intrinsically harmful but it may carry with it certain risks or problems:—

- (i) People who are dependent on cannabis are likely to achieve and maintain higher levels of use than non dependent subjects; if risk attaches to that kind of use, dependent subjects will be at enhanced risk (Troisi et al 1998).
- (ii) The drive toward drug-taking motivated by the dependence will mean that dependent subjects will tend to ignore or play down adverse consequences, educative input, informal pressures from friends or family, and formal social controls.
- (iii) People who become dependent may however eventually not like the state that they find themselves in and the feeling of loss of personal control which is intrinsic to this state. They may then seek professional help with consequent health service costs. So salient has this issue become that the National Institute of Drug Addiction (NIDA) in the USA is currently funding a multi-centre trial on treatment of cannabis dependence, while recent data from the UK's regional drug data base (Home Office 1998) shows that 6 per cent of individuals attending drug agencies in this country today identify cannabis as their primary drug of misuse (1836 new agency contact over a six month period). Reports on people seeking help for the cannabis dependence have come from Australia (Didcott et al 1988), Sweden (Tunving et al 1998) and the USA (Jones 1984).

In sum we conclude under this heading that dependence on cannabis is a clinical reality and one with personal and social implications.



5. *What is the evidence that cannabis in its various forms has valuable medical actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?*

(By Dr R G Pertwee)

Medical uses are also summarised in: Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b.

5.1 As well as having physiological importance, the discovery of the endogenous cannabinoid system has significant pharmacological and therapeutic implications. Indeed, drugs that selectively activate CB<sub>1</sub> or CB<sub>2</sub> receptors (agonists) or selectively block one or other of these receptor types (antagonists) have already been developed. Moreover, one cannabinoid receptor agonist, nabilone (Cesamet®), is currently used clinically in the UK. This drug, a synthetic analogue of  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol, is licensed for use as a suppressant of nausea and vomiting provoked by anticancer drugs. In the USA,  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol itself is prescribed for this purpose and also to boost the appetite of AIDS patients and so reduce or reverse loss of body weight. The formulation used,  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol in sesame oil, is called dronabinol (Marinol®). The introduction into the clinic of  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol and nabilone as antiemetics preceded the development of ondansetron and no clinical studies directed at comparing the efficacy of this excellent new anti-emetic with that of  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol or nabilone have yet been carried out. The licensed use of cannabinoids as antiemetics/appetite stimulants will not be discussed further in this document as it is presumably not a contentious issue.

5.2 As detailed elsewhere (Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b), additional therapeutic uses of cannabinoid receptor agonists may include the suppression of some symptoms associated with multiple sclerosis, with spinal injury and with certain other movement disorders (eg muscle spasticity/spasm) and the management of glaucoma, bronchial asthma, pain and inflammatory disorders. The CB<sub>1</sub> receptor antagonist, SR141716A, may also have therapeutic potential, for example in reducing memory deficits associated with ageing or neurological diseases (Pertwee, 1997a). The evidence supporting the use of cannabinoids for multiple sclerosis and spinal injury, for pain, for primary open-angle glaucoma and for bronchial asthma is particularly promising and is therefore discussed further below or by Dr Rice (pain).

5.3 The evidence that cannabinoids would be effective in relieving spasticity, tremor and pain caused by multiple sclerosis or spinal injury is based on preclinical, anecdotal and clinical data (see Pertwee, 1997b for references). More specifically, animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes, produce marked behavioural changes in motor function, for example hypokinesia and catalepsy, and have significant efficacy in standard tests of antinociception (see also section by Dr Rice). The effects on motor function are no doubt mediated at least in part by the large populations of cannabinoid CB<sub>1</sub> receptors that are present in the basal ganglia of the brain (see para 1.2). Whether cannabinoids produce their putative antispasticity effect by acting at these brain sites remains to be established. There is also good evidence that cannabinoid-induced antinociception is centrally mediated, in this case at sites within both brain and spinal cord (see also section by Dr Rice). In addition, experiments with rats and guinea-pigs have shown that tetrahydrocannabinol can delay the onset and reduce the intensity of the clinical signs of experimental autoimmune encephalomyelitis, a putative animal model of multiple sclerosis. Also relevant is a report that the synthetic cannabinoid receptor agonist, WIN55212-2, can decrease the severity of dystonia in mutant Syrian hamsters with primary generalised dystonia. As to the anecdotal data, these are to be found in numerous newspaper reports and also in responses to a recent questionnaire we distributed to multiple sclerosis patients who self-medicate with cannabis (Consroe et al., 1997). Of the 112 subjects in this survey who were experiencing the following symptoms, the percentage reporting improvement after taking cannabis was 96.5 per cent for spasticity at sleep onset, 95.1 per cent for pain in muscles, 93.2 per cent for spasticity when waking at night, 92.3 per cent for pain in the legs at night, 90.7 per cent for tremor of arms/head and 90.6 per cent for depression. The numbers of subjects reporting these symptoms were respectively 86, 61, 59, 52, 43 and 74. Because this survey targeted multiple sclerosis patients who self-medicate with cannabis, the data it generated cannot be used to predict the proportion of all multiple sclerosis patients who might benefit from cannabis. The clinical data supporting the use of cannabinoids for multiple sclerosis or spinal injury come from seven clinical trials, albeit with rather small numbers of patients. These indicate that cannabis,  $\Delta$ -<sup>9</sup>-tetrahydrocannabinol or nabilone can reduce the intensity of at least some signs and symptoms of multiple sclerosis or spinal injury, particularly spasticity, pain, tremor and nocturia. Additional clinical evidence that cannabinoids are analgesic is described by Dr Rice. Better designed, more extensive clinical trials are now needed that will test the efficacy of cannabis or individual cannabinoids against signs and symptoms of multiple sclerosis and spinal injury more conclusively.

5.4 Raised intraocular pressure (glaucoma), if not checked, will produce irreversible damage to the optic nerve that will eventually lead to blindness. The most common form of this disorder is primary open-angle glaucoma, also known as chronic simple glaucoma. This is characterised by a gradual loss of both visual acuity and peripheral vision, by a blurring of vision and by the appearance of coloured haloes around bright objects. There is good evidence from experiments with animals, healthy human subjects and patients with primary open-angle glaucoma that cannabinoids can lower intra-ocular pressure (Green, 1998). The site and mode of action of cannabinoids for depression of intra-ocular pressure remain to be established as does the question of the optimal route of cannabinoid administration for glaucoma. Cannabinoids can reduce intra-ocular pressure when applied directly to the eye. However, one practical limitation when this route is used is the lack of a suitable drug vehicle. (Vehicles that have been used in experiments induce copious tear



production in human subjects) (Green, 1998). Another potential problem is cannabinoid tolerance as the need for intra-ocular pressure to be kept within safe limits at all times dictates that glaucoma patients be continuously exposed to effective concentrations of their treatment drug.

5.5 Bronchial asthma is often characterised by early and late phase responses. In the early phase response, there is a narrowing of the small tubules in the lungs called bronchioles. This bronchospasm, which produces a marked increase in airflow resistance, may be caused by allergens such as pollen or house dust or by other kinds of stimuli, for example cold air, infections of the respiratory tract or emotional stress. In the late phase response, there is an acute bronchial inflammatory reaction leading to the production of mucus. Cannabinoids show promise for the treatment of the early phase response of asthma. Thus they can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatments of asthma (Hollister, 1986; British Medical Association, 1997). Both cannabis and individual cannabinoids are active when taken orally or when inhaled, either in smoke or in an aerosol produced by a nebuliser or Ventolin inhaler (Williams et al., 1976; Tashkin et al., 1977; Hollister, 1986; British Medical Association, 1997). It is noteworthy that in one study (Tashkin et al., 1977),  $\Delta^9$ -tetrahydrocannabinol administered as an aerosol induced bronchoconstriction, coughing and chest discomfort in 2 out of 5 asthmatic subjects. The mechanisms underlying the bronchodilator effect of cannabinoids remain to be established. However, only cannabinoids with psychotropic properties have so far been found to produce bronchodilation (Hollister, 1986), indicating that the effect may be cannabinoid receptor-mediated. One important priority for any further studies is the development of an improved cannabinoid formulation for administration as an aerosol.

5.6 Like all other drugs, cannabis and cannabinoids can give rise to unwanted effects. However, the known adverse effects of cannabinoids seem to be no worse than those of some accepted therapeutic agents. In one clinical trial with 34 cancer patients (see Pertwee, 1997b), the most commonly reported unwanted symptoms produced by  $\Delta^9$ -tetrahydrocannabinol were dizziness, sedation and dry mouth (more than 75 per cent of subjects), blurred vision (65 per cent of subjects), mental clouding (53 per cent of subjects) and ataxia, numbness, disorientation, disconnected thought, slurred speech, muscle twitching and impaired memory (27 to 44 per cent of subjects). In addition, cannabis may sometimes induce transient confusion, panic attacks, depersonalisation, paranoid delusions and/or hallucinations (Paton and Pertwee, 1973b; Paton et al., 1973; Chopra and Smith, 1974; Tennant and Groesbeck, 1977; Chaudry et al., 1991). Cannabis has also been reported to produce a subtle impairment of postural control (see Pertwee, 1997b).

5.7 Some individuals may be more at risk from the adverse effects of cannabinoids than others (Hollister, 1986; Pertwee, 1997b). For example, cannabis may aggravate existing psychoses and can elevate heart rate. Consequently it would be unwise to give psychotropic cannabinoids to patients with schizophrenia (overt or latent), coronary arteriosclerosis or congestive heart failure. The clinical significance of the ability of cannabinoids to retard foetal development, to induce foetal resorption in animals or to suppress immune function remains to be established.

5.8 Because of the tars and gases produced during the combustion process, smoked cannabis is toxic to airway tissue and probably also carcinogenic (Hollister, 1986; British Medical Association, 1997; Roth et al., 1998). However cannabis is also active orally (see section 2).

5.9 Centrally active CB<sub>1</sub> receptor agonists have the disadvantage of maximizing the incidence of adverse effects by producing indiscriminate activation of all CB<sub>1</sub> receptors. One solution could be to develop drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endogenous cannabinoids so as to increase their concentrations at cannabinoid receptors. This strategy relies on the likelihood that such drugs will not affect all parts of the endogenous cannabinoid system at one time but rather produce effects only at sites where there is on-going production of endogenous cannabinoids. Drugs that inhibit one or other of the processes responsible for the removal of endogenous cannabinoids from the extracellular space already exist (Pertwee, 1998a). This and other possible strategies for improving the benefit to risk ratio of cannabinoids are detailed elsewhere (Pertwee 1996, 1998a,b).

5.10 In conclusion, there is sufficient evidence to warrant additional clinical studies with cannabinoids for the management of several disorders, including multiple sclerosis, spinal injury, glaucoma, bronchial asthma and pain. These studies should be directed at providing objective and conclusive answers to the following questions. First, do cannabinoids have efficacy against selected symptoms that is of clinical significance and, if so, do the benefits outweigh the known risks? Second, does cannabis (or a mixture of two or more cannabinoids) have any therapeutic advantages over individual cannabinoids such as  $\Delta^9$ -tetrahydrocannabinol? Third, is there a significant need for additional drug treatments to manage any of the disorders against which cannabinoids may prove to be effective? Additionally, it will be important to search for better cannabinoid formulations and modes of administration. To succeed, clinical studies with cannabinoids will require adequate funding, the availability of appropriate outcome measures and the committed involvement of scientists and physicians with appropriate cannabinoid and clinical expertise.

5.11 Analgesic effects (By Dr A S C Rice).

5.12 Laboratory evidence of cannabinoid-induced analgesia.

There is a substantial body of evidence from laboratory research which suggests that various cannabinoids possess analgesic effects. However, much of this evidence is based on experiments which examined the responses of laboratory animals to ephemeral noxious stimuli (eg the tail flick test). Whilst of physiological



interest, and heavily utilised in the pharmaceutical industry, these tests are unsatisfactory as models of clinical pain. The results of experiments which employed clinically relevant models of inflammatory (1-4) or neuropathic (neuralgic)(5) pain are now appearing and generally support the concept of cannabinoid-induced analgesia.

Whilst most of the studies of cannabinoid analgesia have examined the neuronal (CB1) receptor, it is now becoming clear that the CB2 receptor may also play a role in analgesia. CB2 receptors are located on cells of immune origin, including mast cells, which are pivotal in the development of the hyperalgesia (tenderness) which develops around an area of tissue injury. Endogenous CB2 agonists attenuate the development of inflammatory hyperalgesia by participating in the process of "autocoid local inflammation antagonism"(1,3,6).

An intriguing body of evidence is emerging which suggest that a proportion of the analgesic effects of the cannabinoids may be mediated by CB1 and CB2 receptors located without the central nervous system (1-3). Exploitation of this effect could conceivably result in the development of cannabinoid analgesics devoid of central nervous system side-effects, but further research is required.

Recent advances in cannabinoid pharmacology (including the discovery and cloning of CB1 and CB2 receptors, the development of specific receptor antagonists and the engineering of genetically modified mice in which the genes encoding cannabinoid receptors are disrupted) have provided tools which will allow further elucidation of the analgesic effects of cannabinoids in the laboratory. More laboratory research is required to fully elucidate the mechanism of cannabinoid-induced analgesia. The experimental tools required to achieve this are now becoming available.

### 5.13 Clinical evidence for an analgesic effects of cannabinoids (7).

For doctors, the current choice of analgesic drugs is essentially restricted to paracetamol, or derivatives of aspirin (non-steroidal analgesics) or morphine (opioids). These drugs are all associated with serious side-effects and are not always effective for the treatment of pain. This is particularly so for neuropathic pain (neuralgia), which is peculiarly resistant to the analgesic effects of opioids. Paracetamol and non-steroidal analgesics exhibit a "ceiling of analgesia" and are therefore only effective in the treatment of pain of moderate intensity. There is thus a clinical need for the development of novel analgesic drugs.

There are numerous anecdotal claims of cannabinoid-induced analgesia. Whilst of some interest, these reports require substantiation, by means of randomised controlled trials in different clinical pain models, before clinical evidence of cannabinoid and analgesia can be assumed. There are only six controlled trials reported in the literature (examining cancer, post-operative and neuropathic pain) (7), these are of poor quality and low power. These studies examined nine tetrahydocannabinol, cannabidiol or levonantradol and four out of the six reported an analgesic effect. Any analgesic effect appears to be similar to that afforded by codeine. Thus, there is currently no reliable human clinical evidence to support nor to refute claims of cannabinoid-induced analgesia. Nevertheless, the data from these anecdotal reports and limited trials does provide some vindication for further clinical study.

The conduct of randomised controlled trials of sufficient power and sophistication, in appropriate clinical models, is warranted to answer the above questions. Such trials are justified by the merging evidence from laboratory study and very limited clinical data. Such trials should examine both analgesic efficacy and side-effects. The precise mechanism of cannabinoid-induced analgesia is unknown and it is presently unclear whether the single molecule approach provided by selective cannabinoid agonists or the synergy of the multiplicity of compounds in herbal cannabis will provide the optimal analgesia. Therefore, both extracts of herbal cannabis (of predictable potency) and the selective cannabinoid receptor agonists should be compared to placebo in appropriately designed clinical trials. The safety of cannabinoids should be assessed before they are used for clinical trials.

## 6. *How strong is the scientific evidence in favour of maintaining prohibition of recreational use? (by Professor J G Edwards)*

6.1 Under this heading our concern is only to show how science can illuminate discussion of the questions rather than ourselves push any particular view. We believe that science can indeed throw light on how this question can be rationally approached and would like to see current public debate much better informed than is at present the case. However, we would at the end of the day expect any such decision to be determined by social and political considerations and that is not territory which we wish to enter. In terms of the strictly scientific input to the debate we wish to identify five relevant postulates:

6.2 *There is scientific evidence to support the postulate that the recreational use of cannabis is not harm free.* We are confident that evidence exists that cannabis can give rise to various types of physical and psychological problems. The confidence with which this assertion can be made will vary with the type of problem being considered and there is room for variation in scientific interpretation. Here is a listing with each potential item bracketed within terms of our own judgement for strength of the evidence for a causal association between cannabis use and that problem on a 5-point scale (5 = very strong, 1 = very weak). In reaching these conclusions we have been much helped by material set out in two recent reviews (Hall et al 1994, WHO 1997). The informal and provisional nature of these ratings needs to be stressed, but this approach may perhaps aid



debate, even if others would give different scores. The scientific evidence on psychological problems has been reviewed in an earlier section of this paper, while for recent authoritative reviews on physical and social pathologies, we would refer to WHO (1998) and Hall et al (1994).

---

|   |   |
|---|---|
| <i>Psychological problems</i>   |   |
| Acute interference with psychomotor function  | 5 |
| Acute interference with short term memory and other cognitive function  | 5 |
| Residual deficit in complex cognitive functioning after cessation of use  | 3 |
| Short-term psychotic disturbance  | 5 |
| Medium-term psychotic disturbance resulting from continued heavy use  | 1 |
| Causation of schizophrenia  | 1 |
| Destabilisation of treated schizophrenia  | 3 |
| Existence of a clinically significant cannabis dependence syndrome  | 5 |
| <i>Physical problems</i>  |   |
| Chronic bronchitis resulting from smoked cannabis   | 4 |
| Cancers of the bronchus and upper airway resulting from smoking cannabis  | 2 |
| Impairment of immune system   | 2 |
| Impairment of foetal development, with small birthright   | 3 |
| Injuries from accident and trauma   | 5 |
| <i>Social costs and problems</i>  |   |
| Cost to mental health services relating to treatment of acute psychosis and dependence and to physical health services due to illness and accident-related trauma | 5 |
| Impairment in school-age scholastic performance   | 2 |
| Impairment in adult work performance  | 2 |
| Contribution to motor vehicle accidents   | 5 |

---

We would expect the list and attached ratings to look very different in, say, five years' time and the pace of research in some but not all of these areas is impressive. We cannot rule out the possibility either of some of what today appear to be adverse consequences later being eliminated from the list, nor the possibility of the evidence strengthening or new problems coming to light.

6.3 *Most individual risks, whether acute or chronic, are likely to have a dose-response relationship with level of cannabis use.* As regards acute effects on psychological and psychomotor functioning of kinds which can be examined in the laboratory, dose-response effects are well established. Although there is good reason to expect that in relation to the list of potential chronic pathologies higher levels of exposure will carry greater risk, these may be risk curves of different shapes or accelerations for different problems and on this type of question there are at present no clear answers. With alcohol it is evident that the risk relationship between drinking and cirrhosis is exponential, for some cancers more or less a straight line, and for coronary heart disease J-shaped (Edwards et al 1994). We do not however know whether doubling an individual's level of exposure to cannabis would less than double or more than double their risk of any of the pathologies set out in the check-list above.

6.4 *Population level exposure of cannabis-related harm will be related to population levels of cannabis use.* Research on population alcohol consumption suggests that across Europe a one litre per capita increase in alcohol consumption will cause a one per cent increase in overall population mortality (Her and Rehm, 1998). We also have a fairly good knowledge of how an overall increase in alcohol consumption is shared out among the drinking population: for an X per cent overall per capita increase in consumption there will be a greater than X per cent increase in heavy drinkers however defined, and a more than X per cent increase in mortality from a pathology such as cirrhosis where the risk function is exponential (Edwards 1994). No parallel knowledge of an exact kind is available on how cannabis use is likely to be shared out among a using population if the supply is increased, but it is reasonable to assume that an X per cent increase in overall use would result in not less than an X per cent increase in heavy use with increase in different problem rates according to the shape of problem-specific risk curve. Population levels of use for this drug are thus likely to have a bearing on public health.

6.5 *Price and access are likely to have an impact on population levels of drug use.* We do not want to go too far in the social science direction, but are aware that considerable econometric research exists on the price elasticity and income elasticity of alcohol (Edwards et al 1994). While similar work on illicit drugs is at a far earlier stage and there is uncertainty as to how the fact of dependence may distort relationships (Bickel and Madden 1998, Bickel et al 1998, Reuter 1998), we would however expect that any cheapening of cannabis would lead to increased levels of use, increased persistence of use, and increased numbers of users. On analogy with research conducted with legislative controls on alcohol (Edwards et al 1994), we would expect weakening of controls over cannabis to result in increased use levels but this is an empirical question on which research at present is not conclusive (Reuter 1998).

6.6 *Within the perspective of what the health sciences have to tell, removal of prohibition on cannabis would have to be described as a voyage into the unknown.* Some added harm and some added costs would undoubtedly result. Whether the impact on the nation's health and safety would be relatively small or whether the consequences would be a damaging endemic of multiple and costly harms or something between these two extremes, is in our view a question which cannot be resolved by reference to existing scientific evidence. It is up to society and government to decide whether there are imperatives that make that risk worth taking, but risky it would be.

**Memorandum by Dr Fred Schon, Consultant Neurologist at Mayday Hospital, Croydon and St George's Hospital**

My submission will deal only with question six. This submission is exclusively my personal opinion.

I have been a full time consultant neurologist for 11 years and earlier in my training I obtained a PhD in neuropharmacology. Until last year I had never had any specific interest in the medical use of cannabis. However, about one year ago a patient of mine with multiple sclerosis developed a severe and disabling abnormality of eye movements which meant his visual world continuously moved up and down. This acquired pendular nystagmus proved resistant to all standard treatments including nabilone. The patient reported a dramatic benefit from smoking cannabis which he said abolished his symptoms.

I therefore set about trying to document this extraordinary observation with the help of one of the leading British experts on eye movements disorders. I discovered quite how difficult it is. My major concern is that it seems completely impossible to obtain permission to do in the hospital what the patient does five times a week at his home, namely to study the effect of smoked cannabis resin.

This is the essential first step in any real scientific enquiry ie, to replicate exactly what the patient does. Instead after about six months I have obtained a licence to study the effect of a capsule containing an oil extracted from leaves of cannabis grown in the UK which may or may not have the same effect.

It seems to me that we do not currently know how many of the alkaloids in the resin are active so to restrict scientific enquiry to just purified individual substances is unscientific. It should be possible to devise a way in which doctors can be given permission under carefully regulated guidance to study smoked resin.

My second area of concern is that I would like to enquire how many other patients with MS with visual problems also have noted beneficial effects of cannabis. As I see it, currently, it is impossible to invite patients through something like the MS Society newsletter to identify themselves. Again it would be realistically impossible to study these patients without the ability to replicate their subjective findings objectively.

**SUMMARY**

1. It is currently almost impossible for practising clinicians to carry out even the simplest clinical studies on the effects of cannabis. It seems essential that some way is found to allow experienced senior clinicians to replicate patients' observations by using smoked resin in the first instance.

2. Some way must also be found of allowing clinicians to identify patients who claim cannabis is beneficial to their condition without legal risk to doctor or patient.

10 July 1998

**Supplementary memorandum by Dr Fred Schon**

Thank you for giving me the opportunity to respond to the Select Committee.

Firstly I would like to reiterate my continuing and intense frustration at being unable to even contemplate submitting for publication what I believe to be highly original observations. The reason being my complete inability to obtain a licence to study my patient, even on a strictly limited number of occasions, when smoking cannabis resin. I am in on-going correspondence with the Home Office on this point.

The answer to Lord Perry's specific question is as follows:

After taking a lot of advice in particular from Dr A Holdcroft I spoke to Mr Alan McFarlane [*Chief Inspector, Home Office AADU*] who has been extremely helpful. He explained that although I wanted a licence to study smoked cannabis resin I was not likely to be able to obtain one. He suggested that if I followed the path used by Dr Holdcroft in her study, namely to use cannabis oil containing capsules and placebo capsules I would be more likely to succeed. I therefore approached Dr Liz Williamson in Professor Fred Evan's department at the London School of Pharmacy who kindly agreed to prepare the capsules which she has done after I obtained my licence.

However I continue to have major problems because so far despite reasonable doses of the capsules they are not having any effect on my patient's symptoms in striking contrast to the smoked resin.

I feel in a "catch 22". On the one hand there is totally understandable pressure to produce scientific evidence to substantiate the medical benefits of cannabis and on the other it seems impossible, at least for me, to obtain



a licence to perform even incredibly simple and straight forward experiments in order to document and then publish the evidence.

*Dr Fred Schon*

*30 June 1998*

#### **Memorandum by Dr Colin Stewart, Dundee Limb Fitting Centre**

I work in the field of major limb amputation which for the most part in the United Kingdom is carried out as a life saving procedure following severely compromised vascular circulation.

1. Following amputation approximately 95 per cent of all amputees have some form of phantom phenomena. This is the feeling that the limb is still there, although in fact it has manifestly been removed.

2. In a smaller proportion of patients, approximately 30 per cent, the phenomena becomes painful and is known as phantom pain. This can take the form of intermittent discomfort or in the extreme, extremely painful shooting pains or burning pain in the limb that is missing.

3. The treatment of phantom pain is extremely difficult and over 50 different treatments have been tried over the centuries.

4. Our current most successful method are the use of psychotropic drugs, including Amitriptyline, Sodium valporate and Carbamazepine.

5. Anecdotal evidence from amputees has indicated that cannabis, when smoked, can relieve this extremely distressing condition and in a survey by Dunn and David in 1974, four respondents report improvement in phantom pain after taking cannabis (*Therapeutic use of Cannabis*, BMA published 1997—ISBN 90-5702-318-0).

6. This small group of patients have to put up with an extremely painful problem for which there is no real satisfactory cure and relief is extremely difficult. Despite the use of the above mentioned medication plus a variety of other pain relieving strategies, including hypnosis and transcutaneous nervous stimulation.

7. The use of cannabis thus may represent an important method of treating this unfortunate group of patients and a limited licence, even for the purpose of a trial basis for this particular condition, would enable us to evaluate its full use and clearly identify whether for this particular condition it would be of value.

I hope the Sub-committee will consider the above and take it into consideration when publishing their deliberations.

*20 April 1998.*

#### **Memorandum by the Young Christian Democrats**

The Young Christian Democrats are the youth wing of the Movement for Christian Democracy, a cross party, non-denominational movement which seeks to bring Christian inspired and biblically based policies to effect in British society. The Young Christian Democrats have a particular responsibility for being a voice for the youth of the movement—and on a broader platform to communicate the views of younger Christians to society in general. The legalisation of cannabis is a subject attracting wide debate amongst young Britons. The Young Christian Democrats believe that legalisation is not the way forward.

#### **1. What are the physiological effects of taking cannabis, in its various forms?**

1.1 Cannabis is composed of “cannabinoids”. Unlike alcohol (which is water based) they are fat based and as a result remain in the body for longer periods of time. Significant quantities can remain in the body for weeks, and traces for months. The cumulative effect of these cannabinoids can seriously damage cells, causing a more rapid onset of cancer than with tobacco.

1.2 The lingering presence of these derivatives also mean that the faculties of the human being are impaired for longer. This means that actions such as driving cars by people under the influence of cannabis (an influence which lasts longer than alcohol) heighten the risk to other members of society due to their lack of control.

#### **2. What are the psychological effects?**

2.1 Every person has a right to life, liberty and happiness. These however cannot be developed in a vacuum. Heavy users of cannabis withdraw from society and this affects their family life and responsibilities and their workplace duties. The use of cannabis creates a lack of self-control which impairs an individual's sense of responsibility to themselves and to society. In addition the individual loses their sense of priority and ability to act rationally. This can lead to actions which the individual may regret or which may have a wider detrimental effect as mentioned above.



### 3. To what extent is cannabis addictive?

3.1 We believe that the use of cannabis is habit forming and creates a psychological addiction. It encourages a lifestyle which fails to recognise the responsibility an individual owes to society. It is necessary for those in leadership to encourage responsible behaviour for the good of society and any moves to decriminalise cannabis for recreational use would send the wrong signal.

### 4. What is the evidence that cannabis in its various forms has valuable medicinal actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?

4.1 It is our understanding that cannabis could be used in the case of Multiple Sclerosis. However detailed scientific research is needed before clinical trials could be taken in order to prove that cannabis either slows down the onset of the condition or promotes recession. If this research proves there is the possibility of aiding the treatment of this condition then clinical trials can be considered.

4.2 We wish to emphasise our belief that the use of cannabis medically and recreationally are separate and distinct cases. The use of cannabis for medical purposes should not promote any legalisation of its recreational use.

Jeremy Tyrrell  
Chairman

7 May 1998

ISBN 0-10-479298-1







**Published by The Stationery Office Limited**  
and available from:

**The Publications Centre**

(Mail, telephone and fax orders only)  
PO Box 276, London SW8 5DT  
General enquiries 0171 873 0011  
Order through the Parliamentary Hotline *Lo-call* 0345 02 34 74  
Fax orders 0171 873 8200

**The Stationery Office Bookshops**

123 Kingsway, London WC2B 6PQ  
0171 242 6393 Fax 0171 242 6394  
68-69 Bull Street, Birmingham B4 6AD  
0121 236 9696 Fax 0121 236 9699  
33 Wine Street, Bristol BS1 2BQ  
0117 9264306 Fax 0117 9294515  
9-21 Princess Street, Manchester M60 8AS  
0161 834 7201 Fax 0161 833 0634  
16 Arthur Street, Belfast BT1 4GD  
01232 238451 Fax 01232 235401  
The Stationery Office Oriel Bookshop,  
The Friary, Cardiff CF1 4AA  
01222 395548 Fax 01222 384347  
71 Lothian Road, Edinburgh EH3 9AZ  
0131 228 4181 Fax 0131 622 7017

**The Parliamentary Bookshop**

12 Bridge Street, Parliament Square,  
London SW1A 2JX  
Telephone orders 0171 219 3890  
General enquiries 0171 219 3890  
Fax orders 0171 219 3866

**Accredited Agents**

(see Yellow Pages)

and through good booksellers

©Parliamentary copyright House of Lords 1998  
Applications for reproduction should be made to HMSO